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MYOCARDIAL INFARCTION

BY

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Weigert (1880) was among the first to recognize infarction of the myocardium and to compare it with similar changes in other organs, for although in 1874 Hilton Fagge had described a series of cases of " fibroid disease " of the heart, which were probably myocardial infarcts, he considered them to be due to syphilis. Despite these observations it was not until some thirty years later that the condition began to attract the attention of clinicians. Herrick (1912) described the clinical features and Pardee (1920) discussed the electrocardiographic changes associated with its occurrence.

Any discussion of myocardial infarction should correlate the pathological changes with the anatomical structure of the heart. In this paper a review of the anatomy of the cardiac muscles and of the coronary arterial tree and the diseases thereof that may lead to muscle infarction is given. The consequences of interference with the blood flow in this tree are then discussed.

MUSCULATURE

It has been known for several centuries (Lower, 1669, and Gerdy, 1823) that the musculature of the mammalian cardiac ventricle does not form a homogeneous mass and can be dissected into several interlacing layers. In the present century (Mall, 1911 ; Flett, 1927; Robb, 1934; Lowe, 1939*a* and *b* and 1940; Robb and Robb, 1942) more detail has been added to the descriptions of the various layers of cardiac muscle in the ventricles, and it is now possible to recognize several muscles in the ventricular wall, which are in reality as distinct as the three glutei muscles making up the gluteal mass. The separation of these muscles was first shown by anatomical dissection, and has been confirmed by the demonstration of independent blood supplies and of their individual involvement in various pathological states (Lowe, 1940).

The musculature of the ventricles consists of two main parts. One, commencing superficially, spirals over the external surface of the heart and twists around itself at the apex of the ventricle (Fig. 1). It then passes upward to form the sub-intimal surface and papillary muscles of the left ventricle. It plays no part in the formation of the intimal surface of the right ventricle, but forms the full thickness of the muscle wall over the apical fourth of the left ventricle. Anatomically this muscle sheet can be divided into two halves, one arising from the sinus region, and the other from the bulbus region of the auriculo-ventricular ring. It is from these points of origin that the two halves take their names—*superficial sino-spiral* and *superficial bulbo-spiral* muscles.

The second main muscle mass (Fig. 2, 3, and 4) forms the deep layers and papillary muscles of the right ventricle, together with the portion of the left ventricle that lies between the pericardial and endocardial parts of the superficial sheet. In this deep mass are three separate muscles. One is confined to the wall of the left ventricle as a cylinder of spiralling fibres,

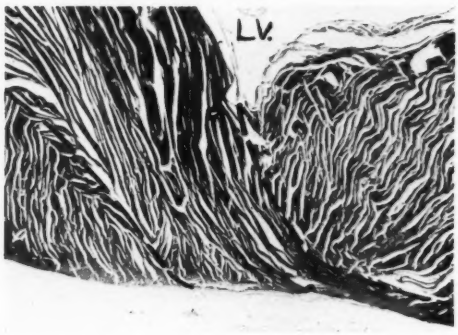

FIG. 1.—Photomicrograph of a longitudinal section through the apex of the left ventricle, L.V., illustrating the vortex formed by the two halves of the superficial muscle layer.

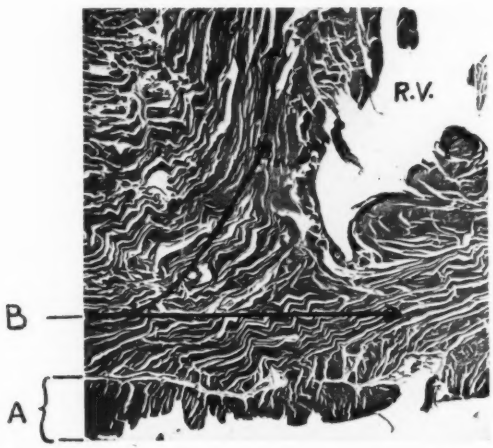

FIG. 2.—Section through the basal end of the interventricular septum showing the superficial muscle layer, (A), defined by a small artery, and the deep sino-spiral muscle, (B), splitting to enclose the right ventricle, R.V.

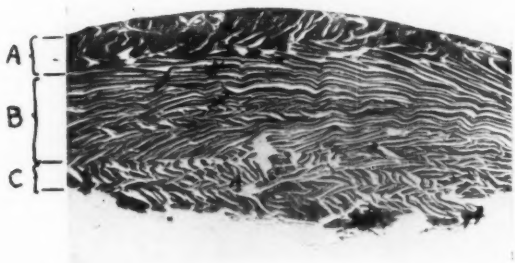

FIG. 3.—Section through the wall of the right ventricle to show the three muscle layers in contrast to the four layers in the left ventricle. (A) Superficial sino-spiral muscle. (B) Layer of deep muscle. (C) Endocardial portion of the deep sino-spiral muscle.

and is known from its site of attachment to the A-V ring as the *deep bulbo-spiral* muscle. The second can be recognized as a spiral sheet that surrounds the left ventricle and splits to enclose the right ventricle and form its innermost and chief muscle layer: the attachment of these fibres to the A-V ring is in the sinus region, and hence this muscle is known as the *deep sino-spiral*. The third encircles both ventricles in a spiral scroll manner, and is called the *scroll* muscle. These three deep muscles are confined to the upper three-quarters of the ventricular muscle mass.

Because of the spiral path of these muscles from base towards apex, it is often difficult to appreciate their independent existence in transverse sections. Unlike skeletal muscles, they are not separated by dense fascial sheets, but only by a small amount of loose connective

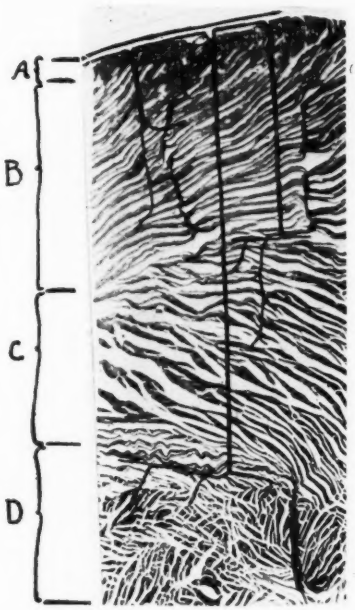

FIG. 4.—Section through the left ventricle near the base showing the four muscle layers. (A) Pericardial portion of superficial layer. (B) and (C) Two of the deep muscles. (D) Endocardial portion of the superficial layer. The peculiar arrangement of the muscular branches of the coronary arteries, by which the parent artery giving branches to the pericardial portion of a superficial muscle gives branches also to the endocardial portion of that muscle but not to the deep muscle in between, is indicated diagrammatically.

tissue. If a transverse section happens to be made in the plane of an artery, then the distinction between the bands may be quite obvious (Fig. 2).

The atrial (auricular) musculature likewise consists of two parts. The superficial consists of a sheet of muscle running transversely over both atria, a few fibres dipping into the interatrial septum. The deep comprises two sets of looped fibres each of which arises from the fibrous ring around the auriculo-ventricular orifice and passes antero-posteriorly around one or other atrium. In addition to these looped fibres, annular fibres surrounds the extremities of the large vessels, the auricular appendages, and the foramen ovale. As the superficial muscles are exceedingly thin, the atrial walls are composed almost entirely of the deep muscle bundles.

CORONARY ARTERIAL TREE

Arising from the sinuses of Valsalva in the aorta, the right and left coronary arteries branch and subdivide to be distributed over the surface of the auricles and ventricles, and later enter

their walls. Some branches lie between the muscle layers in connective tissue planes, whilst others pass at right angles to the surface to reach deeper layers of the wall before they give off branches which run parallel to the surface (Fig. 4). Although there is some overlap in distribution, the right auricle is supplied principally by two branches of the right coronary artery, and the left auricle derives its blood supply from the main left coronary artery and its circumflex branch.

Large anastomotic channels of arterial size between the major coronary branches are easily demonstrated in the hearts of aged people (Gross, 1921). These anastomoses exist at all ages (Lowe, 1937 and 1941), although physiologically they are of much less importance in childhood and youth, and therefore not easily shown by the methods of macroscopic anatomy. Their presence shows they normally carry blood, for if they did not they would disappear as do the umbilical arteries after section of the cord. Pressure difference between the ends of any vessel is the factor that determines the direction of blood flow in that vessel. In a normal coronary circulation arterial anastomoses will have approximately the same pressure at either end, so that the blood flow will be small and may easily change in direction from time to time. In hearts the seat of obstructive arterial changes, marked difference of pressure between the ends of the anastomotic channels can easily occur, and then these vessels enlarge and become visible to the naked eye. It must be remembered that a free anastomosis exists at all ages in all capillary beds.

A study of the traditional descriptions of the fields of supply of the major coronary arteries reveals no unanimity between authors as to the areas supplied. If the right and left coronary arteries are perfused with coloured gelatine solutions of similar viscosity to that of blood and under carefully controlled pressures, the following average description of these fields of supply in the ventricular walls can be demonstrated. The left coronary supplies all the left ventricle except the right third of the posterior wall, and the posterior third of the septum; in addition it supplies the left third of the anterior wall of the right ventricle. The right coronary supplies the anterior two-thirds of the septum and the right ventricle except the portion of the anterior wall just mentioned as being supplied by the left vessel; it also supplies that portion of the posterior wall of the left ventricle already mentioned. There is, however, considerable anatomical variation in the arteries of different hearts so that this description can only be regarded as approximate.

When occlusive arterial disease occurs, these distributions will be upset by opening up of the various arterial anastomoses described. It will then be impossible to predict the field of supply of any one of the major coronary branches.

By injection methods and careful dissection it is possible to show that small coronary branches within the walls supply portions of the various ventricular muscles, but owing to frequent anatomical variations it is of little value to try to determine which branches supply which individual muscle. It can also be shown that in the normal heart the smaller vessels supply one part of one muscle only.

It is of importance in any discussion on infarction to remember that the parent artery, which gives branches to the pericardial portion of a superficial muscle, gives branches also to the endocardial portion of that muscle but not to the deep muscles in between. This is due to the peculiar arrangement of vessels by which some branches penetrate through the thickness of the ventricular wall without giving branches to the muscles of the deep layer through which they pass (Fig. 4). Further, no one arterial branch supplies the whole of any one ventricular muscle.

Diseases of the Coronary Arteries

No essential difference exists between diseases of the arteries of the heart and those of other organs of the body, but because of the vital nature of the tissues concerned, coronary arterial disease often assumes great clinical importance. No matter which portion of the

coronary tree is affected, the gravity of the lesion is largely, if not wholly, determined by the degree of vascular obstruction. The commonest disease that produces vascular obstruction is undoubtedly arteriosclerosis,* which commonly affects the larger arteries in contrast to rheumatic fever, polyarteritis nodosa, and other inflammatory processes, which more often involve the small branches and arterioles.

Arteriosclerosis

Many detailed studies have been made of the incidence of arteriosclerosis at different age periods and of its relationship to coronary artery obstruction (Kirch, 1930, and Wartman, 1933 and 1940), and they indicate that it is a process which is more severe in the latter half of life, although both early and advanced stages of the lesion may be seen in youth (Fig. 5).

The essential pathological change is in the intima, and is characterized by vascularization (Leary, 1935; Paterson, 1938; and Wartman, 1938), cellular infiltration, proliferative changes,

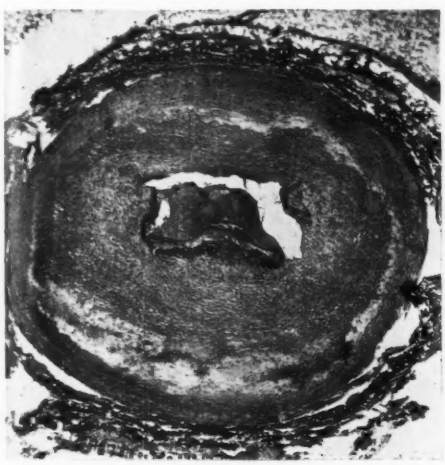

Fig. 5.

Fig. 6.

Fig. 5.—Section of descending ramus of the left coronary artery showing marked stenosing arteriosclerosis and recent thrombosis in an apparently healthy man of 23 years of age. In such cases it is not the mechanical block to the vessel that is important in causing death, but the rate of cessation of blood flow, and the state of the collateral circulation.

Fig. 6.—Macroscopic cross-sections of a stenosed femoral artery which have been cleared to show the vascularization, indicated by arrows, and hæmorrhage in the intima.

and deposition of lipoid, calcium, soaps, and other substances, often giving the appearance of an inflammatory reaction. The intima is greatly thickened at the site of the lesion and not infrequently this produces an appreciable diminution or even occlusion of the lumen. Secondary changes are also seen in the media which becomes thinned with the gradual replacement of muscle fibrous tissue.

Obstruction of the affected vessel may follow gradually by the growth of the intimal changes to such size as to prevent blood flow, or suddenly by thrombosis or hæmorrhage into the intimal (Fig. 6) or medial (Fig. 7) tissues. These hæmorrhages account for about 10 per cent of coronary artery obstructions (Wartman, 1940) and appear to be a sequel to the capillary vascularization of the wall (Moritz and Wartman, 1938; Wartman, Laipply, and Derr, 1943).

Intimal hæmorrhage may cause obstruction either by pushing forward the atheromatous

* The term arteriosclerosis is used in this paper as being synonymous with atherosclerosis, in accordance with the decision of the American Heart Association.

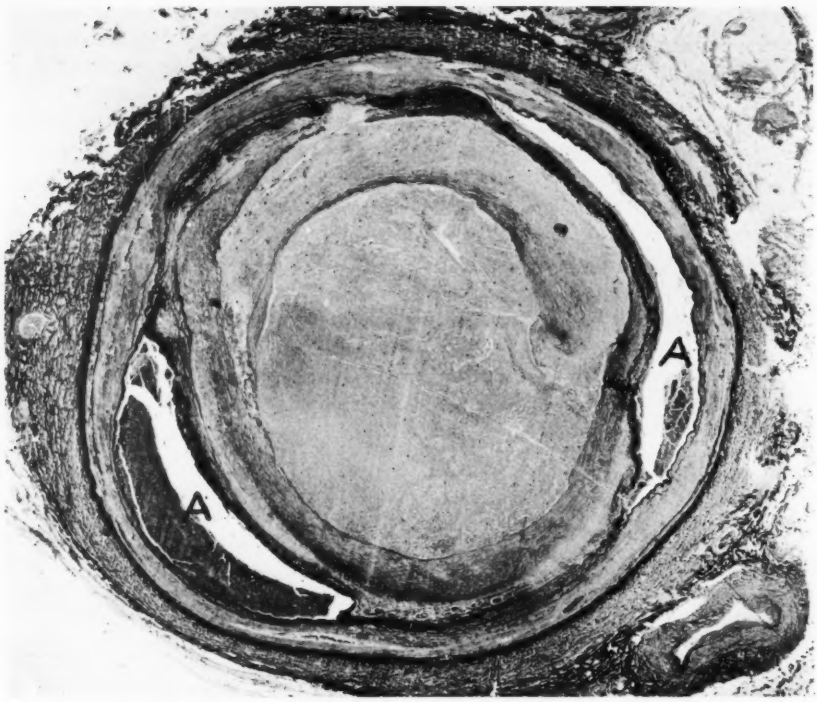

FIG. 7.—Section of a thrombosed popliteal artery to show hematomata (A) in the media. Weigert's and Van Giesen's stains.

FIG. 8.—Section of femoral artery showing a thrombus (T) which has formed at the site of a large intimal hematoma (A). Weigert's and Van Giesen's stains.

plaque into the lumen of the vessel or by destruction of the endothelium, which is followed by thrombosis (Paterson, 1938; Wartman, 1938; Winternitz, Thomas, and Le Compte, 1938; Nelson, 1941) (Fig. 8). Occasionally these hæmorrhages are large (hæmatomata) (Fig. 6) and may bulge externally and even give rise to serious bleeding into the surrounding tissues.

Somewhat similar hæmorrhages are seen in dissecting aneurysms of the aorta, but there they are confined to the media. They frequently start as multiple foci which join and form a channel in the media of the aorta, and this channel may communicate either with the lumen of the vessel or rupture to the exterior. These have occasionally been recorded in the coronary arteries.

Other Arterial Diseases

Other conditions that are occasionally responsible for coronary artery occlusion are the acute and chronic inflammatory arterial diseases and also embolism. None of these are common causes but will be discussed briefly.

Acute Arteritis. This may occur during the course of any acute infectious disease or it may arise by the extension of a neighbouring inflammatory lesion or yet be mycotic in origin. Rare examples of so-called primary or idiopathic acute arteritis have been recorded (Karsner, 1937). Secondary thrombosis on the damaged site produces arterial blockage in these cases.

Polyarteritis Nodosa (*Periarteritis nodosa*). It has been estimated that some 70 per cent of cases of polyarteritis nodosa have involvement of the coronary arteries, and Grant (1940) has indicated that this disease is neither so rare nor so fatal as is generally thought. The histological picture seen in the affected vessels is that of an inflammatory response to some unknown agent. Polyarteritis nodosa usually attacks the small coronary arteries in scattered foci. Resulting infarcts are, therefore, small and disseminated (Fig. 9).

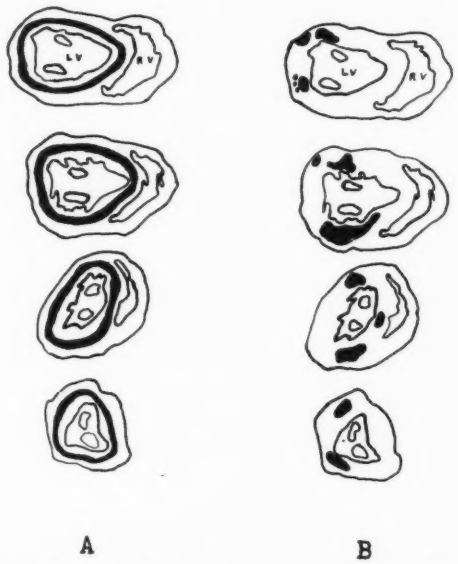

FIG. 9.—Comparison drawings of (A), the deep bulbo-spiral muscle and of (B), the multiple recent infarcts in the myocardium of a case of polyarteritis nodosa. Several small branch arteries were occluded and the infarcts were limited to the deep bulbo-spiral muscle.

Thrombo-Angiitis Obliterans. This is an occasional cause of coronary obstruction (Saphir, 1936), and consists of an inflammatory process in the vessel wall associated with thrombosis. A characteristic, although not universal, feature of the cellular response is the

presence of giant cells and infiltration with small round cells somewhat resembling a miliary tubercle.

Rheumatic Fever. In addition to producing a characteristic inflammatory lesion in the myocardium, this process also produces lesions in the walls of arteries. These are, however, rarely of clinical significance in comparison with the myocardial damage. Involvement of arterioles and small arterial branches is recorded (Karsner and Bayless, 1934) leading to occlusion with small scattered infarcts. Histological study of these vessels reveals no characteristic picture except for the occasional occurrence of Aschoff nodules. Holsti (1927) has recorded a peculiar verrucous endarteritis in which acidophilic material projects into the lumen of the affected vessels and closely resembles the vegetations seen on the cardiac valves.

Tuberculosis. Although tuberculous lesions of coronary arteries can be seen post-mortem (Gouley, Bellet, and McMillan, 1933) in cases dead of tuberculosis, it is of little clinical significance as a cause of coronary obstruction. The arteries are involved either as part of a miliary spread or as a local extension of mediastinal or pericardial disease.

Syphilis. Coronary artery occlusion is a well-established, even if uncommon, sequel of syphilitic aortitis. Obstruction of the coronary vessels usually occurs at the ostia of the arteries in the sinuses of Valsalva, especially if this opening is abnormally high. It is due to thickening of the intima and scarring of the medial coat of the adjacent aortic wall, and occasionally leads to sudden death, for it is a main coronary vessel that is obstructed.

Embolism. One of the rarest forms of coronary obstruction is that due to embolism. The emboli may be fragments of cardiac vegetations or of tumours invading the blood stream. Fat droplets gaining access to the blood stream from bone injuries or gas bubbles entering the circulation through wounds of the neck may also form emboli. Fat embolism is the commonest of these conditions and can be recognized by " streak-like " hæmorrhages in the myocardium. Microscopically fat droplets can be demonstrated in small vessels by appropriate stains. As a cause of death following trauma it may easily be overlooked.

Myocardial Ischæmia

A detailed account of the effects of myocardial ischæmia may now be given under the six following headings.

(1) Infarction of the ventricular wall.
(2) Interference with ventricular function.
(3) Rupture of the ventricle.
(4) Ventricular aneurysms.
(5) Infarction of the auricular wall.
(6) Electrocardiographic changes.

Infarction of the Ventricular Wall (Lowe, 1937, 1940, and 1941*a*). Failure to maintain an adequate blood supply to any part of the myocardium results in death of tissue. This may follow complete or even partial occlusion of one or more coronary branches. Sudden obstruction of a vessel will reduce the hydrostatic pressure distal to the block to a very low level, and create pressure differences across the ends of the anastomotic channels in that area, favouring the passage of blood towards the blocked vessel. If the anastomoses are sufficiently numerous and of sufficient size, they can maintain the circulation beyond the obstruction, and lack of blood supply to the tissue need not result. This, however, rarely happens, for in a normal circulation the sudden obstruction of an artery by an embolus produces spasm of the vessel immediately distal to the block and the flow of blood through these channels is rendered impossible. The immediate effect of sudden blockage of a vessel is therefore to deprive a section of tissue of its blood supply. This causes death of tissue unless it can survive until the spasm passes off. In general, the block will last long enough for death of the essential cells of the cardiac muscle to occur, but the interstitial cells of the fibrous tissue often survive. The size of the block of tissue involved will be determined by the size and situation of the vessel

obstructed, and may vary from a portion of one muscle bundle to portions of several muscles, even to the full thickness of the ventricular wall.

Partial obstruction of a vessel will lower the pressure in the artery beyond the block and again favour the passage of blood through the anastomotic channels. In contrast to complete occlusion there will be no spasm to interfere with the flow of blood into the vessel, beyond the partial obstruction. This results in the establishment gradually, and simultaneously with the developing block, of an adequate anastomotic circulation, so that the final sudden blocking of the partially occluded vessel will have a minimal effect. Thus complete obstruction may, gradually produced, effect no disturbance whatever in blood supply to the tissue. On the other hand, should the parent vessel supplying the anastomotic circulation become suddenly blocked, the area deprived of blood supply will be much greater than that following blockage of a similar vessel in a normal circulation.

If a gradual occlusion developes in several vessels at the same time, then the establishment of the collateral circulation will depend not only on the pressure differences across the ends of the anastomotic channels—this will determine only the direction of blood flow—but also on the volume of blood carried by the parent vessel of the anastomotic circulation. If this vessel is itself partially occluded it will be unable to carry the additional blood to supply the anastomotic circulation and may even fail to maintain an adequate circulation to its normal area of distribution. This will result in portions of heart muscle being deprived of blood supply without complete obstruction to any vessel. These areas will lie at the points farthest removed from their respective parent arteries and the muscle there will be replaced by isolated islands of scar tissues.

Embolism in a coronary artery of a young adult, presumably not the subject of arterial disease, will produce either rapid death or the development of an infarct in the ventricular wall. In general the effect so produced will be greater than it would be in an older person with an established anastomotic circulation.

The following types of infarction may be expected in the ventricular wall:

(*a*) massive infarction, involving the whole thickness of the ventricular wall or parts of several muscles;

(*b*) infarction confined to a portion of one muscle; and

(*c*) scattered small islands of scar tissue.

(*a*) Massive infarction arises from the blockage of a main coronary artery in a normal circulation, or from the obstruction of an anastomotic channel carrying a large amount of blood in a system with occlusive arterial disease. This is exemplified by sudden obstruction of the anterior descending coronary artery—" the artery of sudden death."

Massive infarction may involve the full thickness of the ventricular wall or, if less extensive, portions of two or more muscles (Fig. 10 and 11). These infarcts are frequently wedge shaped with their bases externally. The exact explanation of this wedge shape is uncertain. However, similar wedges may be produced by injecting gelatine media into major coronary branches if improperly balanced pressures are used. It is probable, therefore, that the wedge results from disturbances in the dynamic balance of blood flow through the coronary tree.

(*b*) Infarction of a portion of a single muscle (Fig. 12, 13, and 14) is due to interference with the blood supply through a small arterial branch in the thickness of the ventricular wall. It is not the mechanical block to the vessel that is important, but the rate of cessation of blood flow and the state of the collateral circulation. Although infarction of any portion of a deep muscle has been observed, involvement of the pericardial portion of a superficial muscle is rarely seen.

(*c*) Patchy fibrosis, while it may follow any lesion that destroys muscle tissue in a disseminated, discrete fashion, may be caused by the gradual inability of the coronary circulation to carry enough blood to nourish the whole of the muscle mass. Therefore those parts most

FIG. 10.

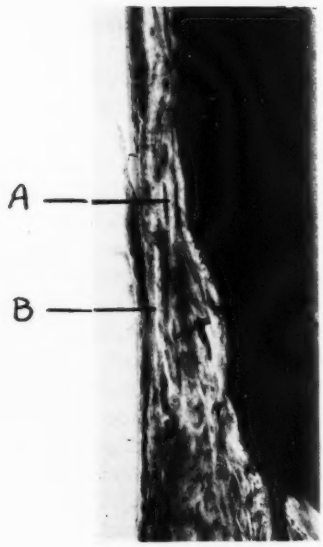

FIG. 11.

FIG. 10.—Aneurysm at the base of the left ventricle.
FIG. 11.—Wall of the aneurysm in Fig. 10 showing the two laminar scars at A and B.

FIG. 12.—Recent infarct involving the superficial muscles at the apex of the left ventricle and the lower end of the interventricular septum, with beginning aneurysm of the septum and mural thrombosis. Note the involvement of the papillary muscle, which is also composed of the superficial muscle bundles.

distant from the source of blood (aorta) will suffer most, i.e. small areas about the ends of arterioles which are supplied by the most obstructed channels.

Interference with Ventricular Function. Broadly speaking, interference with ventricular function can be considered under two headings.

(*a*) Interference with the ability adequately to expel blood. This depends on the amount of muscle tissue killed or damaged, and therefore ceasing to contribute to the force of cardiac

FIG. 13. FIG. 14.

FIG. 13.—Aneurysm at the apex of the left ventricle showing a single laminar scar.
FIG. 14.—Wall of the aneurysmal sac in Fig. 13 showing the single laminar scar, A.

contraction. Following the sudden obstruction of a large vessel not previously constricted, there may be a gross drop in cardiac output and sudden death. If death does not result immediately, and if the damaged area is large enough, there will be a marked fall of systemic arterial blood pressure, and perhaps circulatory failure. This may end fatally, or a balance may occur and some of the anæmic muscle tissues recover, but the fall of blood pressure and circulatory failure that follow massive infarctions are likely to produce a vicious circle and lead to death in a few hours.

The quantity of blood flowing through a vessel is dependent on its lumen, and on the pressure difference across its ends. If the lumen is constant, as it is in many arteriosclerotic vessels, then the quantity of blood carried each minute is determined solely by the pressure differences. With the fall of systemic blood pressure following infarction of musculature, and the inability of rigid vessels to dilate, the area of muscle deprived of blood supply will increase, thus causing a further drop in systemic arterial pressure, and so establish a vicious circle. Frequently the damaged muscle is replaced by scar tissue and the resultant diminu-

tion of muscle means a reduction of ventricular power, manifested by a reduction in cardiac reserve (Lowe, 1941*b*).

The effects produced by the destruction of ventricular muscle depend both on the quantity of tissue destroyed and the particular muscle involved. The superficial muscles play a relatively unimportant part in the production of blood pressure (Robb and Robb, 1939), and destruction of portions of them may be unaccompanied by any circulatory change. By contrast, however, the deep muscles contribute the bulk of the ventricular power and involvement of one of them will produce marked disturbances.

(*b*) Rhythmic activity. If the infarcted tissue is in the interventricular septum, complete or partial heart block may follow. Damaged tissue at the margins of the infarct may act as an irritable focus and ventricular extrasystoles appear. Ventricular fibrillation sometimes develops, and is usually fatal as it is followed by failure of co-ordinated ventricular contraction.

Ventricular Rupture. Rupture of a ventricle may follow destruction of muscle in its wall. If an infarct involves the full thickness of the wall, then tearing of the dead muscle fibres occurs as soon as young granulation tissue appears and the muscle commences to break up. If only portion of the thickness of the wall is involved rupture occurs only occasionally. In such cases hæmorrhage from a large vessel in the damaged area, or communication with the ventricular cavity may allow blood to enter the muscle planes and so dissect a path to the pericardial cavity (Lowe, 1940). Bleeding into the pericardial cavity occurs and death results from pericardial tamponade.

These events usually follow within ten days of the arterial occlusion; after that time the scar tissue replacing the muscle seems strong enough to withstand the tensions developed in the wall, and although it may gradually stretch, it does not give way suddenly.

Aneurysm of the Ventricle. Weakening of the ventricular wall follows replacement of muscle by the inelastic collagen fibres of scar tissue, and the consequences of this are determined by the muscle involved. There may be merely a thinning of the wall or aneurysm formation. Ventricular aneurysms are of two types; basal (Fig. 10) and apical (Fig. 13).

At the apex of the left ventricle the wall is formed by the two layers of superficial muscle and involvement of the superficial musculature at the apex leads to thinning of the wall with the development of a laminar scar. However, if almost the full thickness of the wall is affected an aneurysm will develop (Fig. 13).

As there are several muscle layers near the base of the ventricles, the superficial muscles are unimportant in the production of thinning or aneurysm formation. A study of laminar scars (Lowe, 1941*c*) shows that involvement of a single deep muscle results in thinning of the wall without bulging. The presence of at least two laminar scars in the wall of basal aneurysms of the ventricle indicates that destruction of two deep muscle layers is essential to their formation (Fig. 11).

The physical basis of aneurysm formation is the same in both ventricle and aorta. In both places muscle tissue is active in withstanding pressure, and when enough of it is destroyed and replaced by collagen, gradual stretching and sac formation occurs.

Endocardial thrombosis (Fig. 12) is usually associated with massive infarction or an aneurysmal sac. It is rarely seen when the inner portion of a superficial muscle alone is involved because there is usually no endocardial damage as a thin layer of muscle between endocardium and infarcted tissue frequently survives, possibly deriving its nourishment directly from the ventricular cavity. Emboli may arise from these endocardial thrombi and produce infarction in any viscus as a sequel to myocardial infarction.

*Infarction of Cardiac Auricles.** The principles outlined in discussing ventricular infarcts are strictly applicable to those occurring in the walls of the auricles. In one reported series

* As the term " auricle " is by custom used in clinical and electrocardiographic terminology, it has been retained in place of " atrium " and refers to the whole chamber and not merely to the appendage.

of post-mortem examinations, auricular infarcts were seen 31 times in 182 (17 per cent) cases of ventricular infarction (Cushing, Feil, Stanton, and Wartman, 1942). Most of them were in the right auricle and involved the appendage more often than other parts of the chamber. Endocardial thrombosis was common in these instances and was due to the frequent involvement of the deep muscles of the auricle, which form the bulk of the auricular wall.

Electrocardiographic Changes. Following myocardial infarction electrocardiographic changes occur but their interpretation is difficult (Lowe, 1941*a*). The origin of the cardiac potentials is uncertain, but if, as seems probable, they are produced by the spread of the "impulse" along muscle bundles, and not by a current of action, then until the route of spread of that impulse is known definitely, any interpretation of changes following infarction must be empirical. When muscle is damaged the route of impulse spread is presumably disturbed and the cardiographic tracing will change from the normal, and such a change is likely to be permanent. In addition to this change in route, there will be a current of injury superimposed on the record, but this current is only transitory, and varies from hour to hour, finally disappearing. Non-fatal infarcts rarely involve a very large amount of any one muscle and the permanent disturbance of the electrocardiographic record is often small, whereas the immediate change is often gross.

Attempts to localize the site of infarction by cardiographic tracings must be based on both empirical observations and the anatomical structure of the heart. Most of the investigations so far recorded have considered massive infarctions involving several muscles at various positions in the ventricular wall. There are well-recognized tracings associated with anterior apical and posterior basal infarctions. However, some success has been achieved recently in recognizing tracings corresponding to involvement of single muscle bundles. At present it seems unlikely that any further localization than this is possible, because experimental observations indicate that an injury anywhere along the course of a single muscle produces the same electrocardiographic disturbance.

The disturbances in rhythmic activity of the ventricular muscle are also reflected in the cardiograph as ventricular extrasystoles, heart block, or even terminally as ventricular fibrillation.

Abnormalities in the auricular complex of the cardiogram are present in many cases of auricular infarction. These indicate variations in either the rhythmical activity or disturbance in the path of the impulse through the auricular wall. The former is represented by extrasystoles, fibrillation, wandering pacemaker, or nodal rhythm, and the latter by depression of the P–Q interval ("cupule").

Both in a carefully studied series of human cases (Cushing *et al.*, 1942) and in animal experiments no one of these disturbances was present in every case. Any disturbance in auricular electrical activity may therefore suggest auricular muscle damage—possibly due to infarction.

To conclude this essay we may indicate the directions in which these studies should aid the clinician now and in the future. It will be readily appreciated from the foregoing account of the structure and function of the heart that many of the indications of the existence of a myocardial infarct have a ready explanation. Fall of arterial blood pressure is in most cases due either to the amount of muscle tissue destroyed or to the particular muscle involved. Abnormalities in cardiac rhythm and the electrocardiographic changes will be better understood when sufficient data have been compiled relating to the problems of the electrical activity of the heart. Accurate localization of the specific muscle bundles involved may enable us to predict when rupture of the ventricles or even when congestive cardiac failure is to be expected.

The prognosis of a case of myocardial infarction depends as much upon the disease

causing the arterial block as it does upon the extent of the muscle damage. This factor determines the size of the infarct that follows the obstruction of any given vessel and whether or not a recurrence of the episode is to be expected. The varying condition of the coronary arteries is probably the cause of the great variation in the expectation of life after myocardial infarction—a variation from a few moments to some fifteen years.

A knowledge of the behaviour of diseased coronary vessels is essential in discussing the surgical procedures advocated for improving the myocardial blood supply in coronary artery disease. These procedures aim at establishing new anastomotic channels between extracardiac and cardiac arteries by placing intercostal muscles or omentum in contact with the pericardium. It is assumed in these procedures that the arterial pressure gradient will force blood from the extracardiac to the cardiac vessels. There is however no guarantee that such a gradient will exist. In those cases generally suitable for operative interference the one deficient in blood supply will frequently be deep in the ventricular wall. It is then very doubtful if a satisfactory pressure gradient will exist to transfer any quantity of blood to the heart, and it is possible that the flow will be in the opposite direction. This unpredictable factor probably causes the very variable results that follow these surgical procedures.

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ACUTE LEFT AURICULAR FAILURE

BY

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Various hypotheses have been advanced to account for the occurrence of acute pulmonary œdema in association with mitral stenosis during pregnancy, but none is entirely satisfactory. The following two cases are recorded because they present certain clinical and pathological features that may help to throw some light on the subject.

Case Records

Case 1, *M. H. H.* A primigravida, aged 37, was admitted to hospital, in the fifth month of pregnancy, on account of recurrent attacks of acute dyspnœa with hæmoptysis.

She gave a history of rheumatic fever at the age of seven but, apart from slight shortness of breath on exertion, had been free from symptoms until the third month of pregnancy when she became increasingly dyspnœic and developed a persistent cough with blood-streaked sputum. Two months later she had a sudden acute attack of dyspnœa at rest and coughed up a moderate amount of bright red blood. Three further attacks occurred during the next three days and she was admitted to St. Mary's Hospital, Manchester, under the care of Dr. J. W. A. Hunter, very collapsed, extremely dyspnœic, and coughing up considerable quantities of pink frothy sputum. The radial pulse was only just palpable and there was a trace of œdema at the ankles. Moist sounds were present all over the chest. The blood pressure was 100/70. The clinical picture was that of acute left-sided heart failure. Under treatment her condition improved rapidly and next morning there were only scattered moist sounds in the chest with slight hæmoptysis; the œdema had disappeared and there was no systemic venous engorgement. The heart was grossly enlarged, but its rhythm was regular, and there was a loud apical presystolic but no other diastolic murmur.

With rest in bed her condition steadily improved, the dyspnœa subsided, and the hæmoptysis ceased in a few days. She remained well for two weeks, but then, without apparent cause, became acutely dyspnœic and coughed up a considerable quantity of blood. The suddenness of this relapse suggested the possibility of a pulmonary embolus. She failed to respond to treatment, developed severe pulmonary œdema, and died in a few hours.

Autopsy was performed by Dr. F. A. Langley. The lungs were grossly œdematous, but there was no sign of recent pulmonary embolism, nor of old infarction. The heart weighed 400 g. There was a button-hole stenosis of the mitral valve, measuring 15 × 3 mm. The aortic valve was slightly scarred and the cusps were adherent for a short distance from their bases. The pulmonary and tricuspid valves were healthy. The left auricle was considerably dilated and hypertrophied, its wall being 4 mm. thick. The right ventricle also was considerably hypertrophied, the wall being 9 mm. thick. The pulmonary arteries were moderately atheromatous. Apart from some cortical congestion the kidneys were normal.

The estimated age of the fœtus was 6½ months.

Case 2, *M. McA.* A primigravida, aged 34, was first seen in September 1941 when 4½ months pregnant. She gave no history of rheumatic fever, but had had occasional swelling of the ankles since the age of 15. She had been somewhat breathless on exertion for several years, and more so during pregnancy. On examination there was a coarse apical presystolic thrill, accompanied by a loud crescendo murmur. Moist sounds were present at the base of the lungs, but there was no evidence of right ventricular failure.

A cardiogram showed slight right axis deviation with sinus rhythm. Tele-radiograms showed some enlargement of the pulmonary conus, moderate enlargement of the left auricle, and considerably increased vascular markings in the lungs. A therapeutic abortion was performed at St. Mary's Hospital and she was advised to have no more children.

A year later she was re-admitted to St. Mary's Hospital under the care of Dr. J. W. A. Hunter, as

an urgency, 4½ months pregnant, with right ventricular failure, considerable œdema, and an enlarged tender liver. When seen by one of us (A. M. J.) five days later, the œdema had subsided and the venous engorgement had greatly lessened, but she was still very dyspnœic. The heart rhythm was regular, and there was a coarse apical presystolic thrill accompanied by an exceptionally loud and harsh crescendo murmur. Termination of pregnancy was advised when her condition had improved. Three weeks later she was given 1/3 of a grain of omnopon and 1/150 of a grain of scopolamine prior to therapeutic abortion, and collapsed with very slow respiration. Severe right ventricular failure with gross œdema rapidly developed. When her condition had improved somewhat she was transferred to the Manchester Royal Infirmary (September 30). She was then only slightly dyspnœic at rest, but had œdema up to the groins and in the hands, with free fluid in the abdomen. The percussion note was impaired and there were moist sounds at the bases of the lungs. The blood pressure was 115/75. A cardiogram showed an increased degree of right axis deviation compared with her previous record. Under treatment she improved slowly, but on October 6 she was again given 1/4 of a grain of morphia, and about an hour later became extremely dyspnœic and almost pulseless. With theophylline-ethylene-diamine and atropine she slowly improved, but two days later she aborted. Following abortion her general condition improved rapidly, but she still had extensive œdema and the liver border was two inches below the umbilicus. A few days later the œdema and venous congestion had considerably lessened but her cough had increased and moist sounds were heard in the chest. At the same time she began to have attacks of paroxysmal dyspnœa lasting several hours. On October 20 at 6 a.m. she suddenly became intensely dyspnœic, moist sounds were audible over the whole chest, and she coughed up considerable amounts of frothy sputum. She was pulseless and very cyanosed. With oxygen, atropine, and intramuscular theophylline-ethylene-diamine she improved temporarily but then relapsed and died at 10.40 a.m.

Autopsy was performed by Dr. W. Susman, 24 hours after death. The lungs were œdematous and the right pleura contained about a litre of clear fluid. There was passive congestion of all organs. The heart weighed 260 g.; the right ventricle was considerably hypertrophied, and the left auricle was dilated and greatly hypertrophied. The mitral valve exhibited a severe degree of stenosis, the orifice measuring 5 mm. × 10 mm.; there were small recent rheumatic vegetations on the valve. The aortic valve was healthy but the thoracic aorta showed two patches about 2 cm. in diameter of a pearly grey colour with numerous longitudinal puckerings—appearances suggestive of a rheumatic aortitis. The pulmonary arteries exhibited considerable atheroma. Apart from slight scarring of the capsular surfaces and severe passive congestion the kidneys appeared healthy. The uterus was enlarged (8 × 10 × 3·5 cm.) and the cavity was filled with adherent thrombus.

Histological examination showed diffuse fibrosis of the auricular muscle, and a patchy, mainly perivascular, fibrosis of both ventricles, more severe on the left. The appearances of the aortic lesions were typical of rheumatic aortitis.

Discussion

In 1872 Peter described a typical severe attack of pulmonary œdema occurring during the fifth month of pregnancy from which recovery occurred following venesection and emetics, but which recurred at the same stage of a subsequent pregnancy when he was able to detect characteristic signs of mitral stenosis with a presystolic murmur. His description makes it clear that normal rhythm was present, and in a detailed account of the auscultatory findings he makes no mention of any other diastolic murmur. Thus, in the stage of pregnancy, the presence of normal rhythm, and of a murmur confined to auricular systole, Peter's case resembles those we have described. Subsequently cases were described by several workers, mostly in France and in America (Jensen, 1938).

Two main hypotheses have been put forward to account for the development of acute pulmonary œdema in pregnancy—the "toxic" and the "mechanical." Vinay (1896) described pulmonary œdema in a pregnant woman with chronic nephritis but no heart disease, and a second case, fatal in the fifth month of pregnancy, in a woman with heart disease and albuminuria, which he attributed to renal damage. Pouliot (1904) collected reported cases of pulmonary œdema and found that renal damage was present in many of them. The view generally accepted seems to have been that of Schellong (quoted by Laennec, 1930) that as pulmonary œdema could not be mechanical it must be "toxic." There now appears to be little satisfactory evidence to support the toxic hypothesis, and even in cases of renal disease with hypertension, pulmonary œdema is usually ascribed to left ventricular failure. In our cases, however, there was no hypertension during life and no evidence of renal disease at autopsy.

In left ventricular failure there is no clear dividing line between pulmonary congestion and acute pulmonary œdema; similarly, in mitral stenosis pulmonary congestion and its rarer sequel, acute pulmonary œdema, differ only in degree and are produced by the same mechanism. That mechanism may now be considered.

From his experimental observations on the dynamics of the circulation Wiggers (1923) showed that, under normal conditions, ventricular diastole may be divided into three phases (Fig. 1, A):

(*a*) In *early diastole*, when the mitral valve first opens, the blood flows rapidly from the auricle into the empty ventricle.

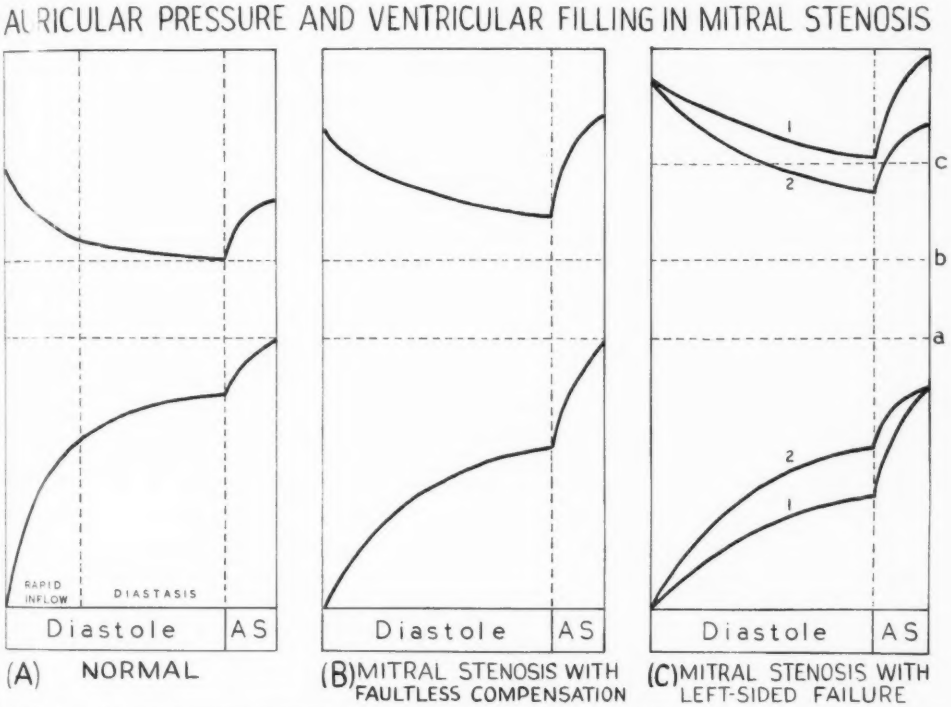

FIG. 1.—The upper curves represent diagrammatically the auricular pressure and the lower curves the ventricular volume during diastole and auricular systole (AS).

a is the volume of the ventricle when filling is complete;
b is the normal auricular diastolic pressure at the onset of auricular systole;
c is the level of auricular diastolic pressure (and of pulmonary venous pressure) which would lead to a rise of pulmonary arterial blood pressure.

(*A*) represents the normal course of events during diastole when the heart rate is slow. During the period of rapid inflow the ventricular volume rapidly increases and the auricular pressure falls correspondingly. During diastasis there is comparatively little ventricular filling. At the onset of auricular systole the ventricle is already almost full, so that the auricle plays only a small part in ventricular filling.

(*B*) represents the events during diastole when faultlessly compensated mitral stenosis is present. Owing to the obstruction to ventricular filling the ventricular volume rises more slowly and the auricular pressure falls correspondingly slowly. At the onset of auricular systole the ventricle is far from full and the auricular diastolic pressure higher than normal. For both these reasons auricular systole makes an abnormally large contribution to ventricular filling.

(*C*) represents the events when left ventricular filling is no longer maintained ("left-sided failure").

1 shows how an increased obstruction at the mitral valve causes slower ventricular filling, and an auricular contribution equal to that in (*B*) fails to bring ventricular filling to normal;
2 shows how the same result occurs when the auricle fails to supply its quota, the mitral stenosis remaining unchanged.

In these circumstances the elevation of the auricular diastolic pressure (and pulmonary venous pressure) above *c* would lead to pulmonary arterial hypertension and right ventricular hypertrophy.

(*b*) In *mid-diastole*, when the initial difference in pressure between auricle and ventricle has been relieved, the blood current is much more sluggish. To this phase he gave the name " diastasis."

(*c*) In *presystole*, when the auricle contracts, the rate of blood flow is again increased.

When the mitral orifice is stenosed, it takes longer to equalize the pressures in auricle and ventricle; consequently the rate of ventricular filling during early and mid-diastole becomes more uniform.

When stenosis is severe the pressure in the auricle remains considerably higher than that in the ventricle throughout early and mid-diastole, and when auricular systole supervenes the auricular wall is still under considerable tension. This, in accordance with Starling's (1918) law, evokes a more powerful auricular contraction, and the dilated auricle develops a compensatory hypertrophy.

As the auricular diastolic pressure rises the pulmonary pressure rises with it, first on the venous side, leading to congestion in the lungs, and later on the arterial side, so that the burden is thrown back upon the right ventricle.

Fishberg (1940) has accordingly described the evolution of mitral stenosis in three stages (Fig. 1, B and C):

(1) *A stage of faultless compensation* dependent on prolongation of the phase of " rapid inflow " at the expense of " diastasis," and auricular hypertrophy.

(2) *A stage of failure of the left side* * *of the heart* with pulmonary engorgement, a rise of pulmonary arterial pressure, and hypertrophy of the right ventricle.

(3) *A stage of failure of the right side of the heart* with systemic venous engorgement.

A case will pass from the first to the second stage if the valvular stenosis increases, or if the compensatory mechanisms break down owing to a weakening of auricular systole or to the onset of auricular fibrillation (Fig. 1, C (1 and 2)). In either event, ventricular filling can only be maintained by an increase of the auricular diastolic pressure. This increase in pressure is transmitted to the pulmonary veins, producing chronic pulmonary congestion and perhaps hæmoptysis. It is usual for the signs of pulmonary congestion to develop gradually, as the slowly increasing stenosis leads to gradual left auricular failure.

In both our cases, however, pulmonary congestion developed suddenly and led to acute pulmonary œdema. A sudden increase of pulmonary venous pressure may be due either to a sudden increase in mitral obstruction or to acute left auricular failure. The former might occur if the mitral valve were suddenly occluded by a ball thrombus, but in our cases no auricular thrombus was present at autopsy.

The possibility of sudden left auricular failure being responsible for the development of acute pulmonary œdema in cases of mitral stenosis depends on the extent to which auricular systole contributes to ventricular filling. Kerkhof's (1936) observations on the cardiac output in mitral stenosis with auricular fibrillation, before and after the restoration of sinus rhythm with quinidine, led him to conclude that auricular contraction was responsible for about 25 per cent of ventricular filling, but in these experiments he made no allowance for the rise in the auricular diastolic pressure associated with fibrillation,† which is an important factor in maintaining ventricular filling. Further, fibrillation is more likely to occur in auricles that have been severely damaged by the original rheumatic infection, and his experiment, therefore, fails to give a true measure of the effect of systole in the more healthy auricle that has never fibrillated. For these two reasons it seems probable that Kerkhof's estimate of the part played by auricular systole is unduly conservative.

This is confirmed by Wiggers and Katz' (1922) observations on the varying contribution of the auricle to ventricular filling at different heart rates. When diastole is prolonged the ventricle is already almost full when the auricle contracts; in these circumstances, auricular

* Presumably Fishberg referred to failure of the left *auricle* since, in mitral stenosis, failure of the left side of the heart could not be due to ventricular failure.

† Unpublished personal observations in experimental fibrillation.

systole accounts for only 10 per cent of ventricular filling. When, however, the heart is beating rapidly, and diastole is short, the auricle contracts when the ventricle is only partially filled; in these circumstances 50–60 per cent of ventricular filling may be due to auricular systole. The effect of mitral stenosis is comparable to that of tachycardia; owing to the reduced rate of blood flow through the mitral valve, ventricular filling is far from complete at the onset o auricular systole, so that auricular contraction becomes correspondingly more important in maintaining ventricular filling.

In our two cases the severe degree of stenosis found at autopsy, coupled with the fact that during life the murmur was confined to pre-systole, suggests that the amount of blood passing through the mitral orifice during early diastole was insufficient to produce a murmur. If this be true, ventricular filling in such cases would be largely dependent on auricular systole. In order to maintain ventricular filling under these circumstances auricular systole must be powerful, and in both our cases the wall of the left auricle was greatly hypertrophied.

In severe mitral stenosis, when ventricular filling is largely dependent on auricular systole, if sudden failure of the auricle occurs, ventricular filling will then depend solely upon an auricular diastolic pressure previously inadequate to effect any substantial filling. Adequate filling can only be re-established if the auricular diastolic pressure rises rapidly. If this occurs, it will lead to a corresponding rise of pulmonary venous pressure, with sudden pulmonary congestion and ultimately acute pulmonary œdema (*Case* 1).

Gerhardt (quoted by Fishberg, 1940) showed in animal experiments that if the pulmonary venous pressure rose above 7 cm. of water the pulmonary arterial pressure began to rise. Thus if the sudden rise of pulmonary venous pressure reaches a sufficiently high level, a sudden rise of pulmonary arterial pressure will follow, and this may lead to acute right ventricular failure (*Case* 2).

The combination of severe mitral stenosis with an efficient auricle is only likely to occur if the original rheumatic infection is associated with severe mitral endocarditis but comparatively little auricular myocarditis, and the infrequency of this combination may account for the comparative rarity of the syndrome. In the majority of cases, acute rheumatic carditis leads to a moderate degree of mitral stenosis coupled with a correspondingly severe lesion of the auricular myocardium, which predisposes to auricular fibrillation. In that case a moderately raised auricular pressure may be sufficient to maintain ventricular filling but if ventricular filling is to be maintained as the stenosis increases, the auricular pressure must continue to rise, so leading to gradually increasing pulmonary congestion. In Table I we have endeavoured to compare the sequence of events in chronic and acute left auricular failure.

TABLE I

LEFT AURICULAR FAILURE

	Chronic	Acute
Mitral endocarditis	+ +	+ + +
Left auricular myocarditis	+ +	+
Mitral stenosis	+ +	+ + +
Left auricular hypertrophy	+	+ + +
Rhythm	Auricular fibrillation	Normal
Left auricular failure	Chronic	Acute
Lungs	Chronic congestion	Acute œdema

Both our patients died in mid-pregnancy and it seems probable that the increasing blood volume and rising heart output at this stage of pregnancy were factors in precipitating heart failure.

SUMMARY

Two cases of mitral stenosis with acute pulmonary œdema leading to death about the middle stage of pregnancy are described.

The mechanism of production of this complication is discussed and it is attributed to acute left auricular failure.

We are indebted to Professor S. L. Baker for the pathological work, which was carried out in his Department.

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CARDIAC INVOLVEMENT IN SPIROCHÆTAL JAUNDICE

BY

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There are relatively few published articles on the cardiac complications of spirochætal jaundice. Our purpose is to review briefly the available papers dealing with spirochætal jaundice complicated by cardiac disturbances, and to report a case.

Reported Cases

Clinical material. Garnier and Reilly (1916) described a case in which an aortic diastolic murmur and a collapsing pulse appeared in the convalescent stage, and assumed that there was a direct involvement of the aorta by the spirochætal infection, in analogy to syphilitic aortitis: this interpretation, however, is hardly acceptable and it is very unlikely that there was any correlation between the aortic regurgitation and the spirochætal infection. Dawson and Hume (1916–17) were the first to report an instance of a cardiac disorder that arose in the course of spirochætal jaundice and appeared to bear a definite relation to it. This occurred in the form of paroxysmal auricular fibrillation which persisted for five days; it was confirmed by polygraphic tracings. Costa and Troisier (1917) observed four cases in which transient dilatation of the heart appeared without any other cardiac manifestations. Marchal, Soulié, and Roy (1935) reported one with transient cardiographic changes consisting of a slight prolongation of the P–R interval and abnormal T waves, and also with a presystolic gallop rhythm and a low blood pressure: no electrocardiograms were reproduced in the original paper and the patient was having digitalis, which makes the interpretation of these findings rather difficult. Clapper and Myers (1943) published two cases with cardiac complications: in one, there was a delayed auriculo-ventricular conduction which lasted seven days; in the other a pericardial friction rub and auricular fibrillation appeared during the height of the illness, persisting respectively for one and two days.

Pathological material in fatal cases in man and in experimental spirochætosis. Mollaret and Ferroir (1935) reported a case in which the autopsy revealed parenchymatous and interstitial changes in the heart, the nuclei showing swelling and chromatoloysis and the interstitial tissue being infiltrated by lymphocytes and polymorphonuclear leucocytes. Beitzke (1916) observed perivascular cellular infiltration in the myocardium. Ashe, Pratt-Thomas, and Kumpe (1941) described a case in which, in the authors' own words, "the myocardium certainly showed severe toxic damage, and although this is common in severe toxæmia, the vacuolization and loss of striation and hyalinization of portions of muscle bundles are suggestive of injury of a type that is rather characteristic of the muscular damage that occurs in Weil's disease." Raun-Byberg (1941) published a case of spirochætosis complicated by fatal myocarditis, but the original paper was not available to us and we are unable to give any details on the nature of the myocardial involvement in this case. Drägert (1934) reported two cases of acute leptospiral vegetative endocarditis in which he was able to demonstrate spirochætes in the vegetations.

Hæmorrhages in the endocardium, myocardium, and pericardium in fatal cases in man and in experimental spirochætosis in guinea-pigs have been observed by several authors. Dawson, Hume, and Bedson (1917) found in inoculated guinea-pigs widespread hæmorrhages in several organs, including the heart, and they were able to demonstrate spirochætes in the heart muscle. Martin and Pettit (1919) observed minute myocardial hæmorrhages in inoculated guinea-pigs and also mentioned the presence of spirochætes in the heart muscle. The presence of spirochætes in the heart muscle in man was stressed by Kaneko (1917). Stokes and Ryle (1916) mention in their paper a fatal case, in the care of Capt. Floor, R.A.M.C., in which the post-mortem examination revealed multiple hæmorrhages in the pericardium. Stokes, Ryle, and Tytler (1917) found hæmorrhages in the heart in two out of four fatal cases; and in inoculated guinea-pigs they found spirochætes in the heart muscle. Watson, McLeod, and Stewart (1935) observed punctiform hæmorrhages in the pericardium in a fatal case; the heart muscle was soft and flabby. Swan and McKeon (1935) found subendocardial and subpericardial hæmorrhages in three out of four fatal cases. Jeghers, Houghton, Rae, and Foley (1935) described hæmorrhages in the pericardium and endocardium in one case. Davidson and Smith (1936) found hæmorrhages in the pericardium in one case and in the endocardium in another; in one of these the myocardium showed fine fatty stippling of the axial portions of the fibres. In a fatal case of Clapper and Myers (1943) the epicardial surface and the endocardial surface over the chordæ tendineæ showed minute hæmorrhages.

Case Report

A seaman, aged 52 years, was admitted to the Newcastle General Hospital on June 24, 1943. His illness started ten days before admission with violent sickness and pain in the legs and the back. Very soon after he became jaundiced. He had fallen into the Thames ten days prior to the onset of symptoms. Except for a syphilitic primary sore in 1918 and malaria in 1926, there was nothing of significance in his previous history.

On admission, the patient looked ill and was deeply jaundiced. The temperature was normal. The lungs were normal, the liver and spleen were not enlarged. The central nervous system appeared to be normal. On physical examination, the heart was found to be perfectly normal, the pulse of good volume and regular, 90 a minute. The urine contained bile and albumin, and the urinary deposit showed some red cells, epithelial cells, and numerous hyaline and occasional granular casts.

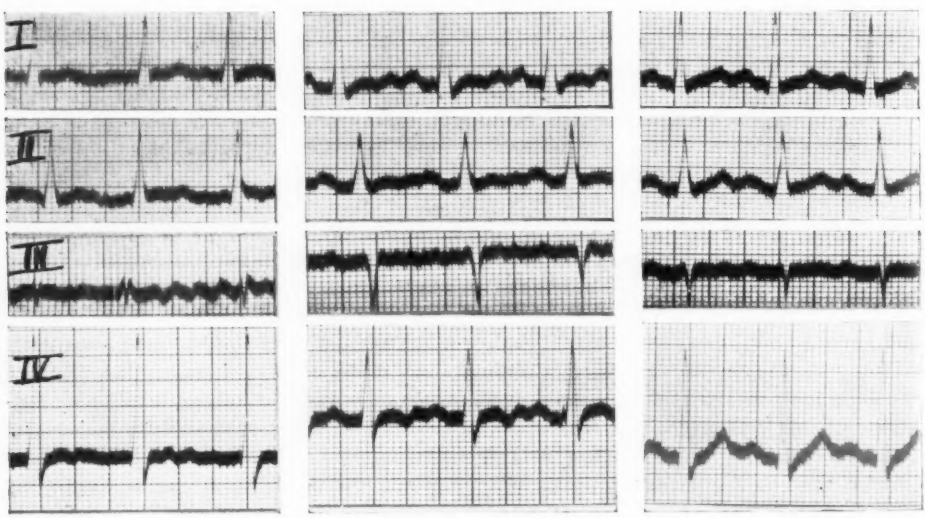

Fig. 1.—(A) Auricular fibrillation, 26/6/43. (B) Sinus rhythm with T wave changes, 30/6/43. (C) Normal tracing, 10/7/43.

The blood urea was 175 mg. per 100 c.c. The Wassermann reaction in the blood was negative. The number of white cells was 7400 per c.mm. The diagnosis of spirochætal jaundice was made and this was confirmed by a positive agglutination titer against *Leptospira icterohæmorrhagiæ* (1 : 1000, 1 : 10,000, and 1 : 30,000 on three different occasions). On June 26, the thirteenth day of the illness, the heart rhythm was found to be irregular and a cardiogram taken the same day showed auricular fibrillation (see Fig. 1A). The blood-pressure was 110/75 and the heart did not seem to be enlarged. The auricular fibrillation persisted for four days and on June 30 there was sinus rhythm with T wave changes and a P–R interval at the upper limit of normal (Fig. 1B). The blood pressure was 105/70 and there was marked asthenia. The heart sounds were distant. The size of the heart appeared to be within normal limits. A third cardiogram, taken on July 10, the twenty-seventh day of the illness, was practically normal (Fig. 1C). At that time the jaundice and the albuminuria were subsiding, but the blood pressure remained low and the temperature was now elevated. The lowest blood pressure reading, 90/70, was recorded on July 14, at a time when the renal signs cleared up completely and the blood urea became normal. Blood pressure, pulse rate, and temperature are charted in Fig. 2. After this the patient's general condition gradually improved, the temperature

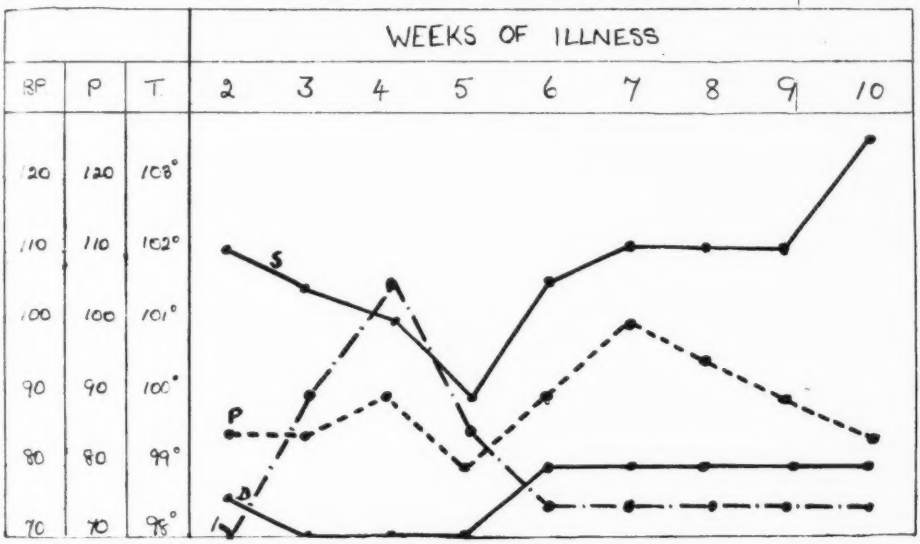

FIG. 2.—S—Systolic blood pressure; D—Diastolic blood pressure; P—Heart rate; T—Temperature. The figures represent the average reading for each week.

became normal, and the blood pressure started to rise, reaching 125/80 before his discharge in a satisfactory condition on August 25. The jaundice completely disappeared by the end of July. A screen examination on August 13 showed the heart to be normal in size and shape.

DISCUSSION

The case reported here showed evidence of a transient myocardial involvement. In the first instance it was the arrhythmia that drew our attention to the heart and prompted us to do electrocardiographic investigations. It is generally agreed that in the absence of disturbances of the rhythm the diagnosis of acute myocarditis is extremely difficult on purely clinical grounds, and as an example Saphir in his remarkable paper on myocarditis quotes Scherf and Boyd stating that " the frequency of myocarditis and the difficulty of its diagnosis are generally appreciated only after electrocardiographic studies of clinical material have been conducted regularly." If more extensive electrocardiographic studies were made in cases of spirochætal jaundice, especially in cases with very low blood pressure and changes in the character of the heart sounds, more instances of myocardial involvement might perhaps be encountered.

In the light of the anatomical findings in fatal cases in man and in experimental spirochætosis in guinea-pigs, the electrocardiographic changes can be accounted for by direct

involvement of the heart, either in the form of multiple hæmorrhages or of direct toxic damage to the heart muscle, or both. Although it is more likely that the electrocardiographic changes in our case and in the cases quoted were due to direct toxic damage to the heart muscle, hæmorrhages in the heart may have been a causative factor. We believe that widespread minute hæmorrhages in the heart, whatever the primary disease is, can produce electrocardiographic changes, especially displacement of the S–T segment and T wave changes. In support of this we mention an unreported case of traumatic asphyxia in a child, aged 5, with bluish discoloration of the chest and neck, widespread petechiæ over the upper part of the chest extending up to the neck, and subconjunctival hæmorrhages, in which we were able to demonstrate marked and transient depression of the S–T segment. We think that in this case the cardiographic changes were caused by subendocardial hæmorrhages. The pericarditis in one of the cases of Clapper and Myers (1943) appeared at a time when the blood urea was 420 mg. per 100 c.c., and it was very probably uræmic in origin. On the other hand, it is unlikely that the high blood urea, so common in spirochætal jaundice, could have been responsible for the electrocardiographic changes observed in the cases reviewed in this paper.

Summary

The papers dealing with the cardiac complications of spirochætal jaundice are briefly reviewed.

One case with cardiographic evidence of transient myocardial involvement is added to those already reported.

The probable causes for the electrocardiographic changes are discussed.

We wish to thank Dr. J. A. Charles, Medical Officer of Health, Newcastle-on-Tyne, and Dr. G. P. Harlan, Medical Superintendent of the Newcastle General Hospital, for facilities provided.

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INCOMPLETE BUNDLE BRANCH BLOCK

BY

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From the Harrogate General Hospital

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Lewis (1925) stated that delay in the passage of the impulse down a bundle branch could alter materially the form of the electrocardiogram. Wilson (1940) defined *incomplete* bundle branch block as due to a conduction defect that merely retards the passage of the impulse through one of the main bundle branches, and stated that it gives rise to electrocardiograms which are " transitional, both as regards the length of the QRS interval and the form of the ventricular deflections between those that represent complete bundle branch block and those of normal outline."

Partial bundle branch block is used to describe curves that contain both bundle branch block and normal complexes. There may be a rhythmic sequence, as in 2 : 1 bundle branch block, or occasional normal QRS deflections may occur in a record predominantly composed of bundle branch block complexes.

In common with the New York Heart Association's nomenclature, Wilson (1944) regards 0·12 sec. as the minimum QRS duration ordinarily compatible with the diagnosis of *complete* bundle branch block. In this country, however, a QRS that exceeds 0·10 sec. has generally been considered as indicating complete bundle branch block providing other criteria are present (Lewis, 1925; and Hunter, Papp, and Parkinson, 1940). This small divergence may be due to a different technique in measurement. In the cases to be described the QRS has been measured straight across at the widest point in any lead. In no case has it measured more than 0·10 sec., when incomplete bundle branch block has been judged to be present.

Case I. A man, aged 58, was admitted to hospital in April 1940 with a history of paroxysms of tachycardia lasting up to 24 hours during the last six months. The B.P. was 220/120. The heart was enlarged to the left. A diastolic murmur of aortic incompetence was audible. The W.R. was negative. He had no paroxysms while in hospital.

After discharge he was seen at intervals as an out-patient, when he said he was well and free from attacks. It was later learnt from his wife that he had had many paroxysms but did not wish to re-enter the hosptial.

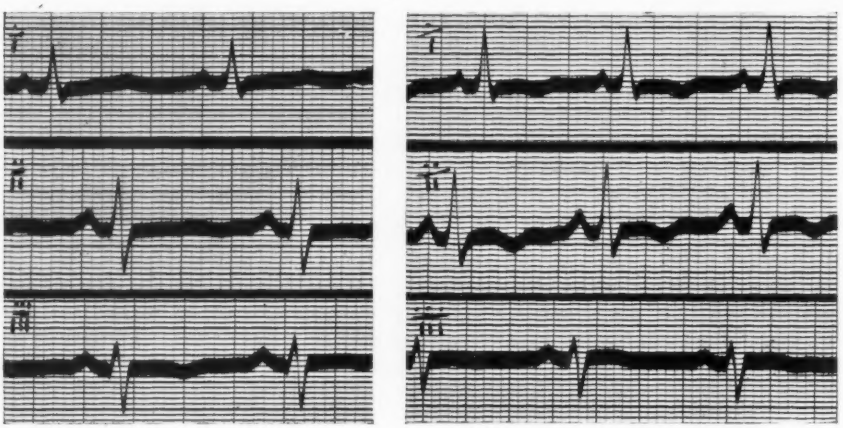
On December 27, 1940, he reported recent nocturnal dyspnœa and œdema of ankles. The pulse was 110 with premature contractions. The B.P. was 230/150. The heart was enlarged to left and right. There was a small effusion at the base of the left lung. The liver was enlarged and tender. The blood urea was 98 mg. per 100 c.c. He was admitted and was given 0·5 mg. digoxin intravenously with 0·5 mg. orally, followed by 0·25 mg. six-hourly. On December 30 the pulse was 160. Following carotid sinus pressure it fell abruptly to 80. At the same time the ward sister reported that she was doubtful how much digitalis he was retaining since he spat out the tablets whenever he could. On the following morning he was worse. The pulse was again 160: the œdema had increased; he was orthopnœic. It was decided to give a further dose of 0·5 mg. digoxin intravenously under electrocardiographic control. Twenty minutes after the injection he was clearly suffering from digitalis poisoning with constant retching and diarrhœa. He was given atropine and morphine but he died the same night.

At *autopsy* (Dr. S. Wray) the heart was greatly enlarged due to hypertrophy of the left ventricle. There was gross atheroma involving particularly the anterior descending branch of the left coronary, which was almost occluded. The mitral and aortic valves showed atheromatous changes on the cusps with some fibrotic contraction of the left posterior aortic cusp. There was gross atheroma of the aorta. The kidneys were granular.

A section of the myocardium supplied by the anterior descending branch shows hypertrophy of the muscle bundles with loss of staining power and cellular outline. The findings suggest that the

hypertrophied muscle has been receiving an inadequate supply of blood due to the arterial atheromatous changes.

Electrocardiograms taken prior to his final admission show that the T waves in leads I and II varied from being upright to a coved inversion. (Fig. 1). This may have been due to variations in



A B

FIG. 1.—*Case* 1. (A) 22/7/40. T I and T II upright. (B) 11/11/40. Bowed inversion of T I and T II.

the blood supply down the anterior descending branch or possibly may be related to the paroxysms of tachycardia. Fig. 2 taken on the day of his last admission shows a ventricular rate of 116. The rhythm is normal except for auricular premature systoles, some having aberrant ventricular responses. These aberrant responses are not confined to the auricular premature systoles but follow normal P waves at the end of lead I. The fourth complex in lead I, also following a normal P wave, has a

FIG. 2.—*Case* 1. 27/12/40. Auricular premature contractions with aberrant ventricular responses. Aberration present also after normal P waves at the end of lead I. The fourth complex in lead I, following a normal P wave, has a deep S wave.

deep S wave. Fig. 3 shows a nodal tachycardia with a rate of 140. Fibrillary waves can be seen, especially in lead III. On account of difficulties with the light the film was thin and another was taken immediately after (Fig. 4). This shows the same nodal tachycardia with fibrillary waves but the duration of the QRS of the alternate complexes in lead I has increased to 0·09 sec. Fig. 5 was taken 15 minutes after the intravenous injection of 0·5 mg. digoxin. The ventricular rate is now 194. Alternation of the complexes is present in leads I and III, giving the appearance of a bi-directional ventricular tachycardia, but the QRS is nowhere more than 0·09 sec. The alternate complexes in lead I are similar to the isolated complex seen in Fig. 2.

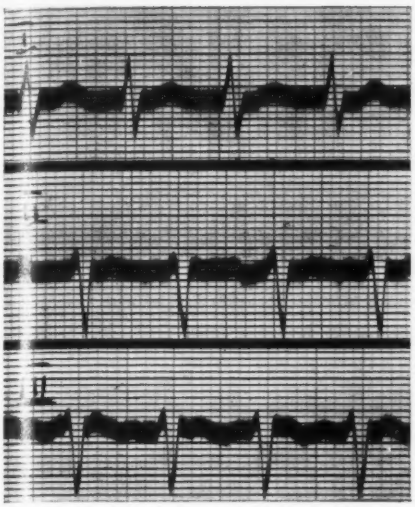


FIG. 3.—*Case* 1. 30/12/40. Nodal tachycardia at a rate of 140. Fibrillary waves deforming the S–T period are visible in leads II and III.

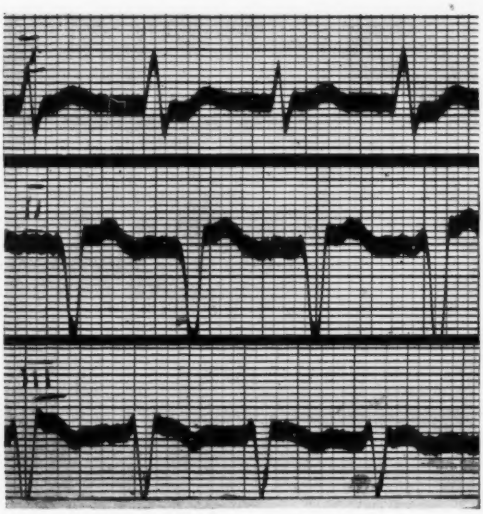


FIG. 4.—*Case* 1. 30/12/40. Nodal tachycardia at a rate of 132, fibrillary waves being seen in lead II. The alternate complexes in lead I have the QRS widened to 0·09 sec.

Comment. Aberrant ventricular responses appeared first following both auricular premature beats and normal auricular beats. One of these had a deep S wave, and was interpreted as intermittent incomplete right branch block. During the early stages of the nodal tachycardia the duration of the QRS of alternate complexes increased to 0·09 sec. without any significant alteration in their shape. Finally the direction of the alternate complexes changed to that of the isolated complex of incomplete right branch block. This gave the appearance of a bi-directional ventricular tachycardia with a QRS duration of only 0·09 sec., but was due to a partial (2 : 1) incomplete right branch block.

Case II. A man, aged 60, was seen first in 1938 on account of dyspnœa on exertion. The pulse was 84; B.P., 144/84. He weighed 14 st. 6 lb. The heart was enlarged to left and right, and he had mitral incompetence. Signs of moisture were present at the bases of the lungs. He was advised to reduce his weight and his activities.

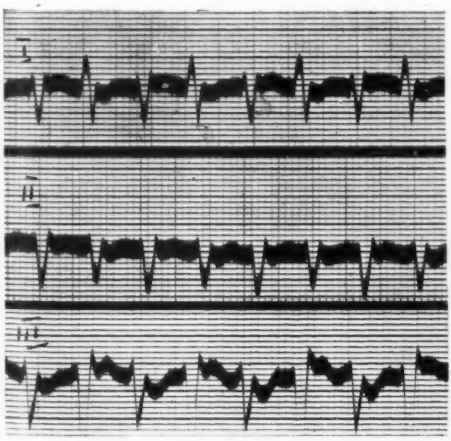


FIG. 5.—*Case* 1.—31/12/40. Nodal tachycardia at a rate of 194, with bidirectional ventricular responses (QRS, 0·09 sec.). Alternate complexes in lead I are similar to the isolated complex of Fig. 2. Partial (2 : 1) incomplete right branch block.

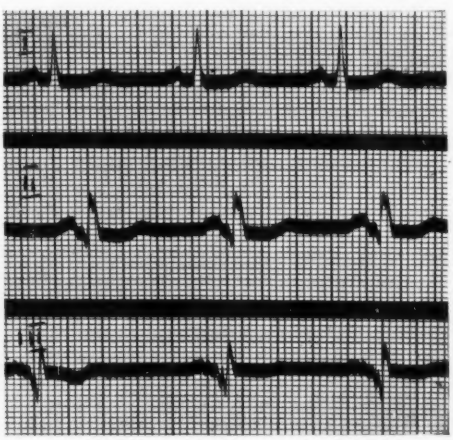


FIG. 6.—*Case* 2. 28/5/38. Small Q and notching of R in lead II (QRS, 0·09 sec.). Lead III, QRS " W " shaped.

In 1940 the size of the heart had increased further and digitalis was commenced in the form of Guy's pill.

In 1942 the auricles began to fibrillate and from that time he required frequent courses of neph al with ammonium chloride to avert congestive failure.

In June 1943 he suffered a cerebral embolism with temporary aphasia and an extensor plant r response on the right side. In the autumn of that year he died suddenly.

The first electrocardiogram taken in 1938 had a Q and a notched R in lead II, the QRS be ng 0·09 sec. In lead III the QRS is also 0·09 sec. and the deflections are " W " shaped (Fig. 6). The comment was made at the time that bundle branch block might soon supervene. This proved in- correct and the curve remained unchanged, except for the addition of many ventricular premat re contractions arising singly and in couples. In 1942, after the onset of fibrillation, the ventricu ar complexes were virtually unaltered, but in lead III the first, third, and last complexes are quite norm al (Fig. 7). Complexes of this type were never seen at any other time. In 1943 a slight widening of the QRS in lead I was observed, although the duration in that lead was still only 0·08 sec. Otherw se there was no change, but " V " leads taken at the same time show a QRS of 0·12 sec. in V.2 with a

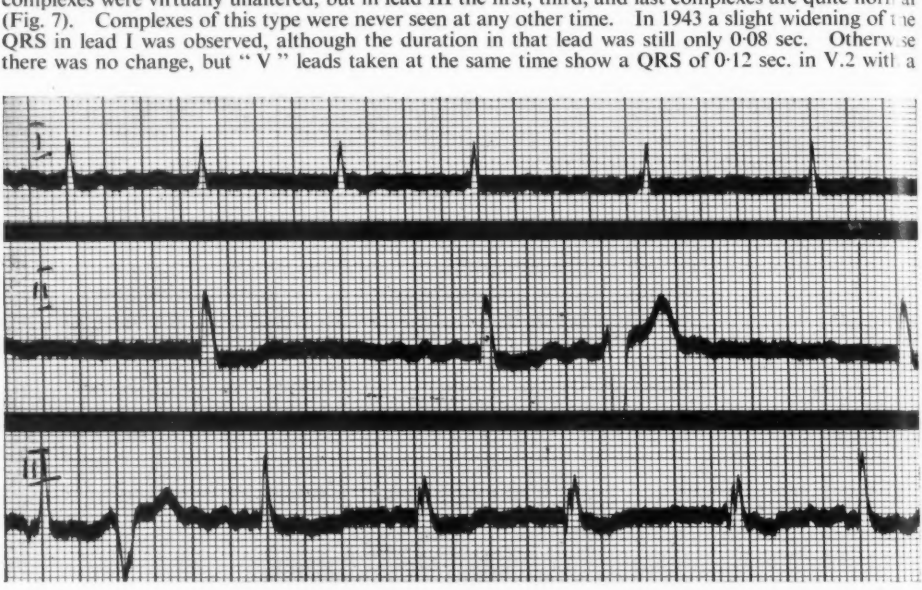


FIG. 7.—*Case* 2. 1/3/42. Auricular fibrillation. Basic complexes unchanged. First, third, and last complexes in lead III normal.

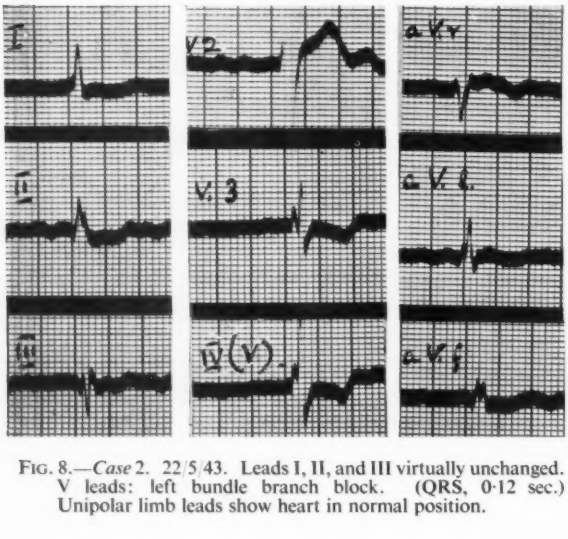


FIG. 8.—*Case* 2. 22/5/43. Leads I, II, and III virtually unchanged. V leads: left bundle branch block. (QRS, 0·12 sec.) Unipolar limb leads show heart in normal position.

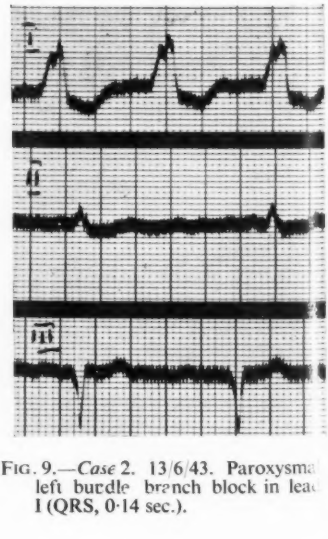


FIG. 9.—*Case* 2. 13/6/43. Paroxysma left bundle branch block in lea I (QRS, 0·14 sec.).

shape characteristic of left branch block (Fig. 8). Two months later—after the cerebral embolus—a paroxysm of left branch block was recorded with a QRS of 0·14 sec. (Fig. 9).

Comment. The normal complexes seen in 1942 (Fig. 7) indicate that his usual curves were due to delayed conduction down a bundle branch. In the following year the " V " leads had the shape of a left branch block with a QRS of 0·12 sec. (the equivalent of 0·11 sec. in limb leads), and a paroxysm of left branch block was recorded two months later.

Case III. A woman, aged 81, was admitted to hospital in November 1941 on account of abdominal pain which had lasted a week. She had been breathless for some months and more recently had been orthopnœic. The pulse was 120 and irregular from auricular fibrillation. The B.P. was 100/80. The heart was enlarged to the left : there were no murmurs. The liver was enlarged and tender. The bases of the lungs were congested. The blood urea was 113 mg. per 100 c.c. The white cells numbered 28,000.

She was given 1 grain of digitalis folia, four times daily, and three days later the rhythm returned to normal. Subsequently she developed a cerebral embolism with a left-sided facial palsy, from which she did not recover.

The cardiogram taken on 7/11/41 shows auricular fibrillation with a ventricular rate of 175. The ventricular complexes have the shape of a left bundle branch block but the QRS is only 0·10 sec.

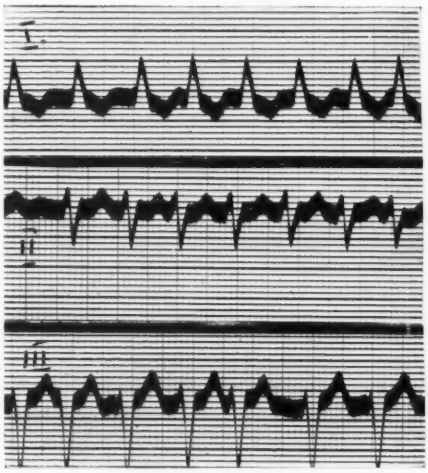


FIG. 10.—*Case* 3. 7/11/41. Auricular fibrillation with ventricular rate of 175. Incomplete left branch block. (QRS, 0·10 sec.)

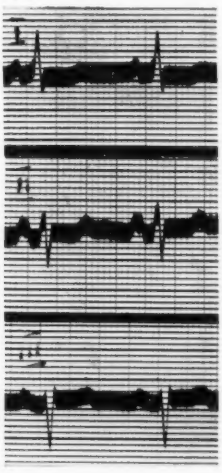


FIG. 11.—*Case* 3. 10/11/41. Left axis deviation. Diphasic T in lead I.

(Fig. 10). Three days later only left axis deviation is present, the QRS duration having returned to normal with the resumption of normal rhythm (Fig. 11).

Comment. The first cardiogram conforms in all respects to a left bundle branch block except that the QRS is insufficiently widened. It was interpreted at the time as indicating advanced left axis deviation or possibly incomplete left bundle branch block. The first alternative was negatived by the second record.

Case IV. A man, aged 69, was admitted to hospital in 1938 on account of dyspnœa, cardiac asthma, and œdema. The B.P. was 200/110. The auricles were fibrillating. The heart was greatly enlarged to left and right. The blood urea was normal. The W.R. was negative.

He was given digitalis and injections of salyrgan with ammonium chloride, but the congestive failure was only partially relieved and he died three months later.

Several cardiograms were taken showing auricular fibrillation and inversion of T in leads I and II. In one record (Fig. 12) intermittent bundle branch block complexes occurred in leads I and II: their shape is of *Type A* right branch block with a QRS of 0·10 sec. A fortnight later intermittent branch block complexes were again seen in leads I and II: these had the shape of the wide SI pattern and the QRS was 0·12 sec. (Fig. 13).

Comment. The intermittent right branch block is unstable since the shape of the complexes changes. The QRS duration of 0·10 sec. in those of the first record is insufficient for complete bundle branch block.

Case V. A man, aged 74, was admitted to the surgical side of the hospital on 8/7/42 with retention of urine. He had spent the greater part of the last two years in bed on account of shortness of breath

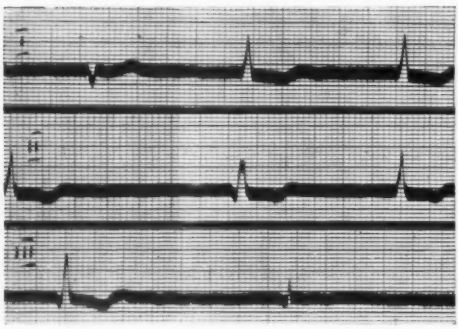


FIG. 12.—*Case* 4. 10/8/38. Auricular fibrillation with diphasic T waves in leads I and II. First complex in leads I and III and second in lead II have the shape of a "Type A" right bundle branch block with QRS of 0·10 sec.

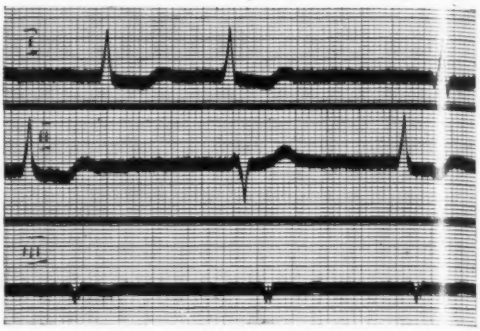


FIG. 13.—*Case* 4. 24/8/38. Third complex in lead I and second in lead II wide SI pattern of right bundle branch block. (QRS, 0·12 sec.)

and œdema of the legs. He had been given digitalis, but the dosage is not known. The pulse was 100 and irregular from auricular fibrillation. The B.P. was 130/90. The heart was greatly enlarged to right and left. There was œdema of the legs. The blood urea was 57 mg. per 100 c.c. The leucocytes numbered 18,000. A supra-pubic intubation (Mr. Pearce) was performed on 27/7/42. On August 1, since the rate had increased, 1 grain of digitalis folia, t.d.s. was started. This was reduced a fortnight later to 1 grain daily, and he was discharged free from œdema in September.

The first cardiogram taken on 21/7/42 (Fig. 14) shows auricular fibrillation with a partial left bundle

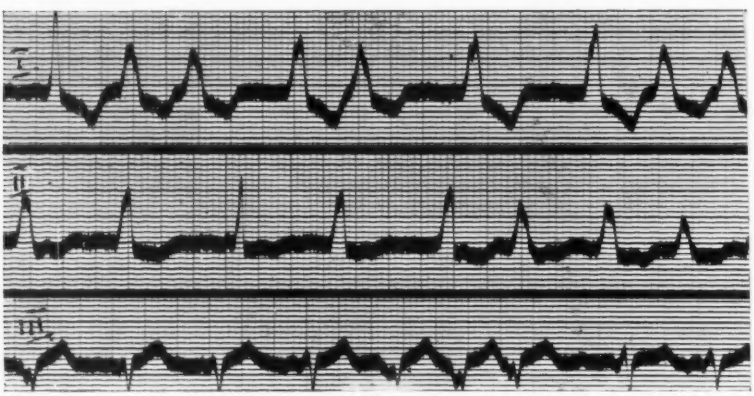


FIG. 14.—*Case* 5. 21/7/42. Auricular fibrillation with ventricular rate of 100. Partial left bundle branch block. (QRS, 0·12 sec.) Complexes with normal QRS duration being present in all leads. B.B.Bl. complexes vary in shape.

branch block (QRS, 0·12 sec.). There is considerable variation in the shape of the ventricular complexes, and the first complex in lead I and the third in lead II together with some in lead III have QRS deflections of normal duration. In Fig. 15 (18/8/42) the QRS deflections have all a normal duration with the exception of the first two in lead I in which the duration is 0·10 sec. Auricular fibrillation persists with left axis deviation. By 10/9/42 normal rhythm has returned and the ventricular complexes have assumed a form intermediate between the two preceding curves with a QRS duration of 0·12 sec. (Fig. 16).

Comment. The QRS deflections in the first cardiogram varied considerably in shape apart from the normal complexes. When the rate was slowed with digitalis the duration of the QRS became normal but transitional complexes (QRS, 0·10 sec.) occurred. Finally bundle branch block returned, having a form intermediate between the general shape of the first record and the left axis deviation of the second.

Case VI. A woman, aged 74, was admitted to hospital on 11/1/44 under the care of Dr. Glyn Reah, who kindly afforded facilities for observation. The auricles were fibrillating. The B.P. was

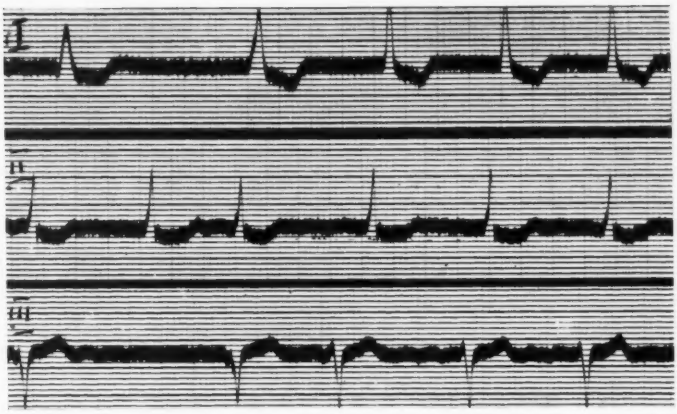


FIG. 15.—*Case* 5. 18/8/42. Auricular fibrillation. Left axis deviation with inversion of T in lead I and depression of S–T in lead II. The QRS of the first two complexes in lead I is 0·10 sec.

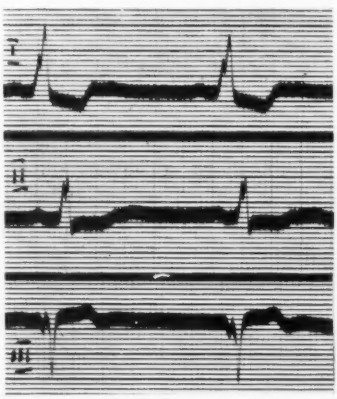


FIG. 16.—*Case* 5. 10/9/42. Normal rhythm. Left bundle branch block. (QRS, 0·12 sec.) Shape of complexes differs from those in Fig. 14.

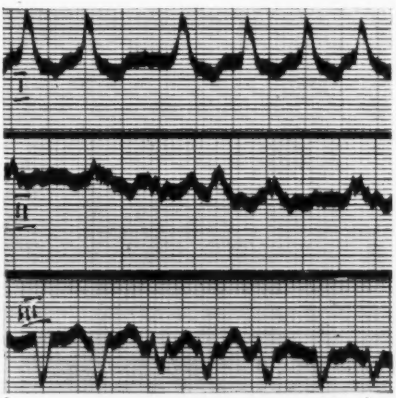


FIG. 17.—*Case* 6. 13/1/44. Auricular fibrillation with ventricular rate of 160. Left bundle branch block (QRS, 0·11 sec.)

100/60. The heart was enlarged to the left, and there was mitral incompetence. Crepitations were present at the bases of both lungs, and the liver was enlarged and tender. Since she had received no digitalis for the previous fortnight, it was decided to obtain a rapid effect by means of digitalis lanata. Accordingly 8 c.c. of cedilanid was given intravenously and slowing occurred within thirty minutes. Four days later normal rhythm returned, and two days later she suffered an embolism into her right leg. From this she made a satisfactory recovery without embolectomy.

The first electrocardiogram (Fig. 17) shows auricular fibrillation with a ventricular rate of 140. Left bundle branch block is present with a QRS duration of 0·11 sec. Fig. 18 taken 35 minutes after

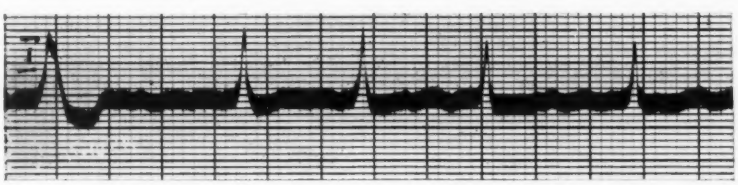


FIG. 18.—*Case* 6. 13/1/44. Lead I, 35 minutes after cedilanid, 8 c.c. intravenously. QRS now normal except first complex.

cedilanid shows a ventricular rate of 104, and the QRS deflections have returned to normal, except the first in the lead. Fig. 19 (17/1/44) shows the return of normal rhythm. All the ventricular complexes with the exception of the last two in lead III (which resemble the normal complexes shown in Fig. 20)

FIG. 19.—*Case* 6. 17/1/44. Lead I. Nodal rhythm at rate of 100 : no evidence of auricular activity : incomplete right (wide SI pattern) B.B.Bl. (QRS, 0·10 sec.) Lead II. Nodal rhythm at 96: P waves deforming the S–T interval of alternate complexes. Incomplete right B.B.Bl. Lead III. P waves move forward from S–T till S–A node takes control at fifth complex when QRS returns to normal.

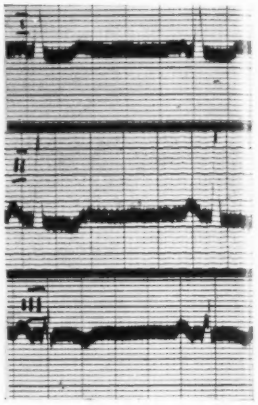


FIG. 20.—*Case* 6. 20/1/44. Normal rhythm. Normal QRS. Digitalis depression of S–T.

are of the wide SI type of right branch block but the QRS does not exceed 0·10 sec. In lead I there is no evidence of auricular activity, the rhythm arising from a centre in the A-V node with a rate of 100. In lead II inverted P waves can be seen deforming the S–T interval of alternate complexes. In lead III the rate has fallen to 90 and P waves can be made out in each complex. The first deforms the S–T interval, the second is almost buried in the QRS: then P moves forward until the auricle gains control of the rhythm in the fifth complex. At that point the ventricular complexes change and become normal. Later the curve reverted to partial left branch block (QRS, 0·12 sec.), normal complexes being present in leads II and III (Fig. 21). Then the duration of the QRS increased to 0·14 sec.,

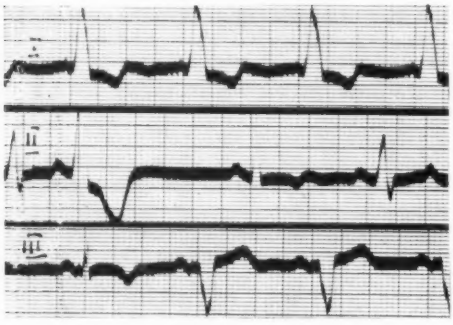


FIG. 21.—*Case* 6. 22/2/44. Partial left bundle branch block. (QRS, 0·12 sec.) Normal QRS follows premature systole in lead II. Normal complex also seen in lead III.

FIG. 22.—*Case* 6. 24/2/44. Left bundle branch block (QRS, 0·14 sec.). Transitional complex (QRS, 0·10 sec.) follows compensatory pause in lead I.

and Fig. 22 shows a transitional complex with a QRS of 0·10 sec. after the compensatory pause of a premature ventricular systole. Later again the ventricular complexes became normal.

Comment. This case shows unusual instability of the bundle branch block. The following changes were noted. Left branch block (QRS, 0.11 sec.): normal deflections after intravenous digitalis; incomplete right branch block (QRS, 0·10 sec.) shortly before the resumption of normal rhythm: normal QRS deflections; partial left branch block (QRS, 0·12 sec.): left branch block (QRS, 0·14 sec.) with a transitional complex (QRS, 0·10 sec.); normal QRS deflections.

Discussion

In *complete* bundle branch block the speed of conduction down one branch of the bundle is so much slower than down the other that the impulse passes across the septum to activate the ventricle on the affected side. In *incomplete* bundle branch block the difference between the two sides is less. The affected ventricle may receive the impulse partly from across the septum and partly via its own branch, or else, when the difference is slight, wholely via its own branch though with some delay. Alternatively there may be delay in conduction down both branches caused by " a general depression of the conductivity of the Purkinje tissue " (Wilson *et al.*, 1944) and the delay may be approximately equal on both sides. Such cases might be expected to show a slight increase in the duration of the QRS with minimal changes in the shape of the complexes, and nothing to show a predominant lesion in either branch. These changes are sometimes seen in the aberrant ventricular responses that often follow premature auricular systoles, or are found in auricular tachycardia or flutter (Slater, 1930).

There are thus three groups: those with bilateral bundle branch delay, shown by a widened QRS without axis deviation (Case 1); those with delay in either right or left branch (Cases 1, 2, 3, 4, and 6); those showing a combination of the two (Cases 5 and 6).

In Case 1 slightly widened QRS deflections occurred first after auricular premature systoles, and later at every alternate beat. There was little alteration in the shape of these complexes and they are likely to be due to delay in conduction down both branches.

The last curve of Case 1 showed a bidirectional type of tachycardia with alternate complexes pointing downwards, and the same shape was seen earlier in an isolated complex following a normal P wave. Bidirectional tachycardia has been recorded in digitalis poisoning by Schewnson (1922) and by Luten (1925). Luten suggested that the rhythm originated from a point near the bifurcation of the main stem, and that there was impairment of conductivity down each branch alternately. However, the sequence of events in Case 1 all point to delay down the right branch only.

In Cases 3 and 4 and in the episode of right branch block in Case 6 there is no doubt as to the side affected. The curves conform in every particular to left and right branch block respectively except that the duration of the QRS is 0·10 sec. Had not normal complexes been present, either in the same record or a few days later, they might have been interpreted as showing advanced axis deviation and ascribed to hypertrophy of the muscle. This type of incomplete branch block may, therefore, be more common than is supposed. In Case 2 the standard leads, although abnormal, did not indicate any axis deviation, but the chest leads showed delay down the left branch.

Transitional complexes provide the most reliable evidence of incomplete bundle branch block, since, in the absence of complete A-V block with independent ventricular centres, they cannot be due to anything else. They are rare, being found in only two of the thirteen cases of paroxysmal bundle branch block studied by Comeau, Hamilton, and White (1938). But the branch block in Cases 5 and 6 was unstable, both showing partial branch block at times. Case 6 had no fewer than five changes in the duration of the QRS, which ranged from 0·08 to 0·14 sec. A similar example was recorded by Herrmann and Ashman (1930). In Case 5 the branch block complexes varied in shape in the first cardiogram, and differed again after the resumption of normal rhythm.

The duration of the QRS deflections in these transitional complexes was 0·10 sec. and, especially in Case 6, they did not show much axis deviation. The transitional complex in Case 6, too, occurred during a phase of left branch block (QRS, 0·14 sec.) and followed an episode of incomplete right branch block (QRS, 0·10 sec.). They are, therefore, probably due to the combined effect of a bilateral delay, accounting for some of the widening of the QRS, with additional delay down one branch leading to a moderate axis deviation, the proportion of each varying in different cases.

Summary

Six cases of incomplete bundle branch block have been described. In none did the duration of the QRS exceed 0·10 sec. when incomplete bundle branch block was judged to be present. In all of the cases normal complexes have been present for comparison, either in the same record or within a short period.

The evidence suggests that the cases could be divided into three groups.

The first shows a slight increase in the QRS without axis deviation as exemplified by the aberrant ventricular response to an auricular premature systole. These are probably due to a bilateral delay down each main branch (Case 1).

The second shows delay down one branch, fulfilling the criteria for bundle branch block except that the QRS does not exceed 0·10 sec. (Cases 1, 2, 3, 4, and 6).

The third shows transitional complexes (Cases 5 and 6). In these cases it is likely that the transitional complexes were due to a combination of bilateral delay down each main branch with additional delay down one branch, since both cases had an unstable branch block which sometimes changed from right to left, and there was not much axis deviation although the QRS duration was 0·10 sec.

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THE PLACE OF FOLIANDRIN WITHIN THE GROUP OF CARDIAC GLUCOSIDES

BY

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The need for a home-grown cardiac glucoside has made itself felt in increasing measure during the last few years, and as a consequence a great number of plants of this country have been studied and tested for their possible content of cardiac principles. Popular medicine and the oldest botanical, i.e. biblical, literature helped to discover the way that promised the quickest success and eventually led to the pharmaceutical utilization of the leaves of the oleander bush (*Nerium oleander*).

The wild Palestinean oleander bush belongs to the species of *Apocynaceæ*, containing in its leaves a glucoside which could be isolated in a pure crystalline form. The crystals are arranged in colourless tufts, the melting-point being 245°. The glucoside is optically active, rotating polarized light to the left.

Amorphous as well as crystalline substances had already been extracted from oleander leaves. Schmiedeberg (1883) was probably the first to isolate various principles from those leaves. He distinguished between neriin, nereantin, and oleandrin. Pharmacologically, he found that neriin and oleandrin exhibited a digitalis-like activity so that he called the former oleander-digitalein. French authors (Pieszcek, 1880; Leulier, 1889; and Dubigadon-Durieux, 1911) also reported isolation of cardiac principles from the bark of the Algerian variety of oleander.

Windaus and Westphall (1925) undertook the chemical analysis of these amorphous and crystalline substances. But it was not before Flury and Neumann's successful isolation of a pure crystalline product from oleander, in 1935, that the path was smoothed for the study of the chemical constitution. The results of these studies can be summarized as follows: oleandrin is optically active, rotating the light to the left, and upon hydrolization yields an aglycone, the oleandrigenin, which is identical with acetyl-gitoxigenin. Moreover, a sugar-residue, the "oleandrose," is split off, in which, however, none of the sugars so far known to play a part in digitalis chemistry could be identified (Shoppee, 1942).

The physical and chemical data reported by various authors for the sorts of oleandrin hitherto isolated show much divergency; this should not, however, surprise us if we consider that the habitat of the various oleander species as well as the technical methods used also show wide variations. Certain differences have even been established between the pure oleander glucoside manufactured in this country, the foliandrin, and that described by Flury (1935). Thus, for example, foliandrin has its melting-point at 245° as compared with 249° given by Flury. One cat-unit of foliandrin is equivalent to 0·324 mg./kg., while for Flury's principle it is 0·25 mg./kg.

Clinical application also revealed differences between these two sorts of pure oleander glucosides. Thus a complete and lasting digitalis effect is attributed to Flury's principle, while the specific cardiac effect of foliandrin appears with surprising rapidity with no need

for cumulation, particularly with reference to the auriculo-ventricular conduction. It acts, in addition, as a powerful stimulus to diuresis. Two electrocardiograms from a man, aged 56, who suffered from heart failure, may serve as an illustration of the foliandrin effect in the human subject. Clinically, his heart had been found enlarged in all directions. At the time of examination, pulmonary infarction was, moreover, diagnosed. In the first there was auricular fibrillation at a rate of 190 a minute (Fig. 1, A). After he had been given foliandrin

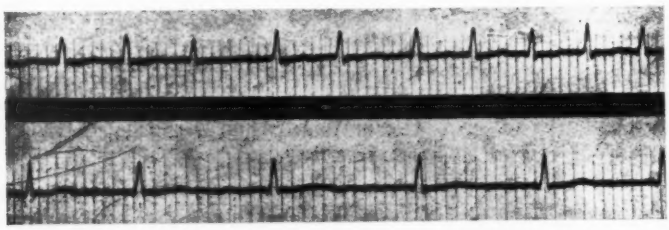

FIG. 1.—The effect of foliandrin on auricular fibrillation. (A) Before, (B) after a fairly full course by mouth.

for two days (4 × 50 drops per day)—which, in fact, is very near to the tolerance dose—followed by 4 × 1 foliandrin suppositories, the pulse rate dropped to 120 a minute on the third and to 90 a minute on the following day (Fig. 1, B).

Analysis of the clinical effect meets with a certain amount of difficulty. The time when the drug is given, the particular pathological stage, extra-medicinal factors influencing the treatment, etc., often play so vital a part that the effect of a certain principle must necessarily be different in every individual case. As clinical studies alone did not suffice, other methods had to be looked for to make it possible to assign the place to foliandrin within the group of cardiac glucosides. We tried, therefore, to get the necessary information from the reactions seen in the cardiogram of a cat after injection of one cat-unit of foliandrin. There is some diversity of opinion as to what should be deduced from the cardiographic changes occurring after administration of cardiac glucosides. The number of authors who consider the changes appearing after digitalis administration (lengthening of the P–R interval, inversion of the T wave, etc.) a specific effect of the drug is probably just as large as the number of those who attach less importance to them (Weese, 1936; Cattell and Gold, 1941; Moe and Visscher, 1938; Walther, 1904; and Brams, 1929). With due allowance for divergencies arising from the different methods, the following may be accepted. Allowing for certain variations due to dosage, anæsthetic method, and the duration of the action of the drug, the shape of the cardiogram may well be considered as characteristic, as regards the decrease in height or inversion of the T wave, the bowl-type or angulated-type of depression of the R–S–T segment, etc. These changes do not, however, suffice nor do they show a sufficiently high degree of reliability to allow of definite conclusions as to the therapeutic or toxic dosage (Gold *et al.*, 1931) of the glucoside or as to morphological changes of the heart muscle (Dearing *et al.*, 1943). However, there are two characteristic features that are, indeed, able to give information on the quality of the cardiac glucoside in question, viz. the onset of sinus bradycardia and of ectopic beats, especially if the doses employed are those established as fatal for the particular experimental animal.

This is corroborated by two papers published quite recently. In the article published by Dearing, Barnes, and Essex (1943) the great number of variations of the electrocardiogram appearing upon administration of the various cardiac glucosides are set in relation to morphological changes of the heart muscle. Krueger and Unna (1942) followed up these changes over the whole period during which the glucoside effect took place, grouping them according to the nature of the glucoside as well as to the doses administered. They used for this purpose a recently devised " heart-rate recorder " which made it possible to trace the frequency and

regularity of the heart beat on an ordinary lamp-black kymograph. They found two main differences between the effect of digitoxin (Merck) and ouabain (Merck): ouabain reduced the heart rate as early as after 15 per cent of the fatal dose, while with reference to digitoxin, reduction of the sinus rhythm occurred only after roughly 30 per cent had been injected. Similar data were established by Bauer and Reindell (1938) by Walther (1940) and by Robinson and Wilson (1918) with a different experimental method. Another difference between the effect recorded after digitoxin and ouabain was the appearance of " irregularity of heart beats." Krueger and Unna pointed out that with digitoxin, cardiac irregularity made its appearance after 76 per cent, and with ouabain after the administration of 58 per cent of the fatal dose. It should, however, be borne in mind that the anæsthetic method employed may be the cause of deviations of up to 2 per cent. The data so far published concerning the " cardiac-irregularity dose " are 70 per cent (Planelles and Werner, 1923) and 68 per cent of the fatal dose (Bauer and Reindell, 1938).

The two characteristic features referred to above—reduced heart rate and the appearance of arrhythmia—can be objectively established, and if artificial stimuli, as strangulation or cooling, are eliminated, the changes are, in fact, only attributable to the glucoside administered. Objective recording of these changes is possible by cardiographic tracings. We, therefore, chose this method to ascertain the position of foliandrin within the group of cardiac glucosides. Since for foliandrin—provided that a certain experimental method is adhered to—the fatal dose has been established as 0·324 mg./kg. ±S.E. of 0·019 which is equivalent to one cat-unit, it was a simple procedure to arrange for intravenous injections that would contain a quantity sufficient to produce systolic syncope in the experimental animal.

Methods and Results

Cats weighing from 1·5 to 3·5 kg. received intravenous injections into the femoral vein of one cat-unit of foliandrin respectively in urethan anæsthesia (1·8 g./kg.) and the development of the cardiac action was followed up in the electrocardiogram until death occurred. We always took the second lead (left foreleg—left hindleg). The required quantity of foliandrin, was prepared from a stock solution containing 40 mg. of foliandrin per 100 c.c. in 96 per cent alcohol. Normal saline was added to make the volume up to 10 c.c. for every injection The time during which the solution was injected was always the same, 5 minutes. After 15. 25, 50, 75, 90, and 100 per cent of the fatal dose had been injected, a cardiogram was recorded and the further development followed up oscilloscopically. As soon as particular rhythmic changes made their appearance, tracings were again taken. Thus it was possible to record the entirety of the events taking place in the cat's heart from the beginning of the injection until its death. An illustration of this method, so far tried in 6 cats, is shown in Fig. 2. We only accepted the onset of slowing of the heart-rate and irregularity of the beats as an indicator of the foliandrin effect. On purpose we do not enter into detail as to the changes of the T wave or of certain intervals.

The reactions taking place in the cardiac muscle and auriculo-ventricular conduction system, if syncope is produced by foliandrin, are shown in the 12 cardiograms of Fig. 2, which were taken from a continuous 15 m. long film.

The results of the above studies show that (1) reduction of the heart rate occurs as a result of intravenous injection of foliandrin which sets in after 15 per cent of the fatal dose (=one cat-unit) has been introduced, and (2) the first signs of irregularity of the heart beat appear after 50 per cent of the fatal dose (=cat-unit) has been given.

The following table gives the data for digitalis, ouabain, and foliandrin with reference to the above mentioned signs.*

* Experiments conducted by us with digitoxin " Roche " and strophantin (Burroughs Wellcome) have, essentially, yielded the same results as those published, although the number of data at our disposal is too small to allow of definite conclusions.

Signs	Percentage of fatal dose after which signs appeared		
	with digitalis	with foliandrin	with ouabain strophantin
Slowing of heart rate	30	15	15
Irregularity of the heart beats	70	50	60

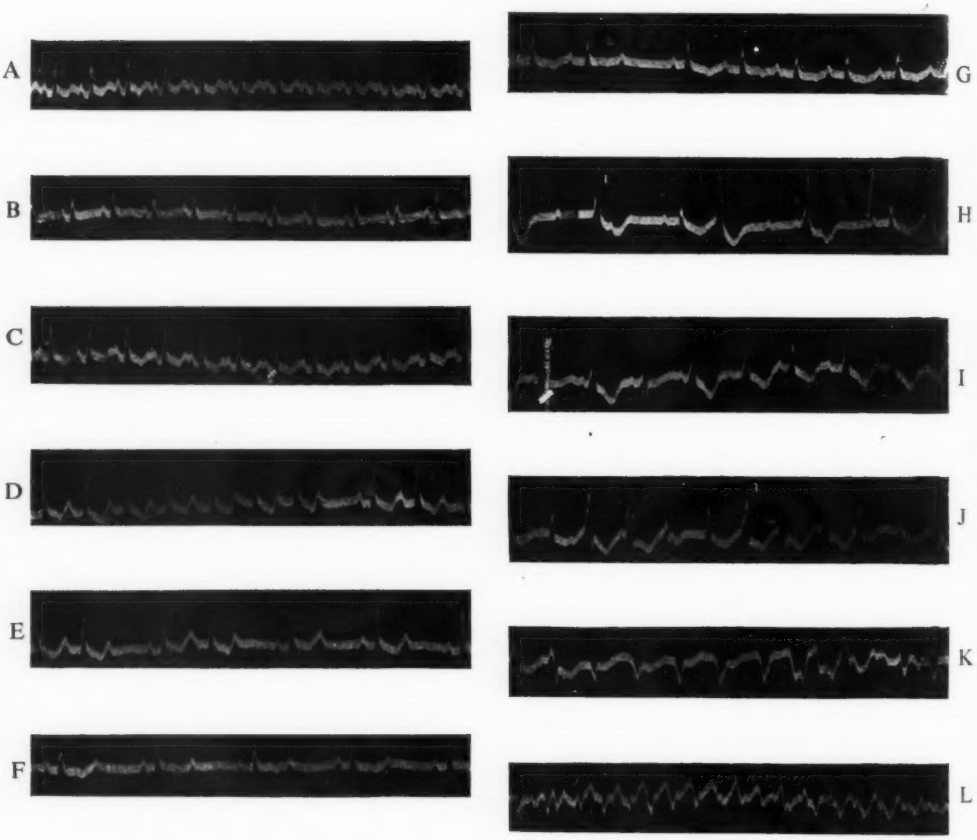

FIG. 2.—Twelve cardiograms taken on a continuous long film from a normal cat (A) Before the administration of foliandrin. (B)-(F) After the administration of various percentages of the fatal dose (=1 cat-unit). (B) After 15 per cent with some reduction of rate. (C) After 25 per cent. (D) After 50 per cent. (E) After 75 per cent, showing the first signs of irregularity. (F) After 90 per cent. (G)-(L) Terminal stages after 100 per cent fatal dose (=1 cat-unit).

Comparing the results obtained with digitalis, ouabain, and foliandrin, we may conclude that the oleander glucoside foliandrin is very closely related to ouabain, in any event belonging to the category of the strophantin glucosides rather than to that of digitalis.

These results gain particular importance in a clinical respect. Strophantin is so rapidly and completely broken down in the intestinal tract that practically no cardiac effect can be expected after oral administration, while for foliandrin clinical experience has shown that the full cardiac effect may be produced by oral administration, and that the specific effect occurs

very rapidly. It should be included in the strophantin rather than in the digitalis group, and should, therefore, be considered a " strophantinoid." As far as we know, therefore, foliandrin is the first glucoside of this group to develop its full cardiac activity in the peroral route.

The drug has so far been tested on human patients in the Hadassah University Hospital, Jerusalem, the Hadassah Municipal Hospital, Tel-Aviv, and the Government Hospital, Haifa and Jerusalem. Results will be published elsewhere.

Summary

The pure glucoside foliandrin isolated from the Palestinean oleander bush (*Nerium oleander*) distinguishes itself very definitely from principles so far isolated from various oleander species. Apart from other chemical as well as physical characteristics, it could be shown by means of continuous electrocardiographic tracings from a cat's heart, that upon intravenous administration its action is identical with that of the principles belonging to the group of strophantin (ouabain) glucosides and the drug should therefore be considered a " strophantinoid." In contradistinction to strophantin, it displays its full cardiac activity upon peroral administration.

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TEMPORAL ARTERITIS

BY

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Temporal arteritis is a rare condition. The earliest reported cases are those of Horton, Magath, and Brown (1932) who described identical histological changes in the temporal arteries of two cases. Five years later these same authors described five additional cases. The first English papers are those of Curtis Bain (1938) and Jennings (1938). More recently the number of reported cases has been increased to some twenty by those of Bowers (1940); Sprague and MacKenzie (1940); Dick and Freeman (1940); Gilmour (1941); Hoyt, Perera, and Kauvar (1941); and Sproul (1942).

Little or nothing is known about the ætiology of temporal arteritis, and perusal of the reported cases substantiates the view that the disease is of a chronic infectious nature and is not related to either tuberculosis or syphilis. The condition occurs most often in the fifth or sixth decade and is commonest in women. Its principal symptom is headache, chiefly referred to the site of the affected vessels, and the pain is not only intractable to the usual remedies, but is also aggravated by mastication or by other movements of the jaws and face. The involved vessels feel thickened and nodular and gradually become devoid of pulsation. The disease lasts over a period of several months and most patients recover. Diagnosis rests upon a biopsy of the affected vessels, and sometimes the mere resection of a portion of the affected vessels seems to have relieved symptoms.

Horton, Magath, and Brown cultivated a strain of actinomyces from a portion of resected vessel, but did not believe that this was the cause of the disease. Sproul and Hawthorne (1937) and Gilmour (1941) showed that identical lesions may be present in the aorta and its branches, and the latter named the condition giant-cell chronic arteritis. This at least dispels the original and usual view that temporal arteritis is a localized and non-fatal malady, and indicates that temporal arteritis is but a local manifestation of a diffuse arterial disease. Among other sites where similar lesions have been described are the occipital, retinal, and radial arteries. It seems probable that the intractable headache of some cases may be due to involvement of the cerebral vessels. There does not so far appear to be any explanation for the predilection for the temporal arteries in this disease.

The histological picture of the published cases is remarkably uniform, and is that of an arteritis. The intima is greatly thickened and there may be thrombosis in the markedly reduced lumen of the vessel. The media is largely replaced by granulation tissue with fragmentation of the elastic lamina. Characteristically present in the media are giant cells with many nuclei.

REPORT OF A CASE

A. M., a labourer, aged 61, complained of rheumatic pains in the knees and shoulders for six months, and of severe headaches in the temporal and occipital regions for one month. His past history did not include any severe or important illness.

His present illness was ushered in gradually with pain in the knee and shoulder joints, and a general feeling of weakness, so that he found it difficult to get about. After a few months there was

spontaneous improvement in his joint symptoms, but he began to have very severe headaches involving the sides and back of his head. The headache was aggravated by movements of the jaw, by coughing, and by mastication. Coincidently he noticed small tender nodules on his temples and over the occiput. The headache persisted with unabated severity and remained uninfluenced by any usual therapy. There was no disturbance of vision.

FIG. 1.—Low power view of part of a transverse section of the artery. (Stained hæmatoxylin and eosin; magnification ×250.)

FIG. 2.—High power view of part of the same section showing a typical giant cell. (Stained hæmatoxylin and eosin; magnification ×550.)

On examination he appeared to be rather thin and pale. Moderate arteriosclerosis was present. The heart was normal and the blood pressure 150/80. The lungs were emphysematous. The pupils reacted to light and to accommodation and the fundi were normal. The reflexes were all present and equal. There was some muscular wasting of the arms and legs. The joints were not swollen but coarse crepitus was present in knees and shoulders.

There was marked tenderness over the occipital and temporal areas of the scalp, particularly the latter. A number of small nodules were clearly visible and palpable over the temporal artery and similar nodules were palpable over the occiput. The temporal artery was thickened and pulsation was diminished. The nodules appeared to be in the walls of the vessel, and they were exquisitely painful on palpation; the skin overlying them was reddened. In the course of three weeks the pain subsided and the nodules disappeared. In the final stages pulsation in the affected vessels was barely apparent.

Laboratory Examinations. Blood sedimentation rate was 13 mm. in 1 hour (Westergren). Blood urea 60 mg. per 100 c.c. The red cell count was 3,670,000 per c.mm.; the hæmoglobin was 62 per cent (Haldane); the colour index 0·8, and the white cell count 7200 per c.mm. The Wassermann and Kahn reactions were negative. An electro cardiogram showed normal axis and no abnormality. An X-ray of the chest was also normal.

An initial diagnosis of periarteritis nodosa was made, but in the absence of any evidence of visceral involvement a biopsy of the temporal artery was performed, and a segment of the vessel removed. The course after operation was uneventful.

Pathological Report. The material submitted consisted of a small piece of an artery with grossly thickened wall, and a lumen that was practically occluded. The tissue was fixed in formalin, and transverse sections were prepared and stained by hæmatoxylin and eosin, Van Gieson's stain, and Verhoeff's elastic tissue stain.

Histologically, well-marked pathological changes were present, and these were found to conform very closely with the histological picture of temporal arteritis as described by Horton and Magath, and with the histological picture described in other arteries by Gilmour, and named by him giant-cell chronic arteritis.

The intima showed great hypertrophy, and the hypertrophied tissue was composed of proliferating muscle fibres supported in a mucoid ground substance. The cells in this tissue were arranged quite irregularly and the more usual arrangement into circular and longitudinal bundles was entirely absent. The elastic lamella was fragmented and in certain areas it could not be demonstrated. In a few areas in the intima giant cells could be seen, but they were very few as compared with those in the media, and much smaller in size.

The media showed chronic inflammatory changes with lymphocytic infiltration and giant-cell formation. These giant cells showed very large numbers of nuclei and appeared to be of foreign body type for the most part. In appropriately stained sections it could be seen that in some instances these giant cells were in intimate relationship to small fragments of elastic tissue.

The changes in the adventitia were relatively slight as compared with those in the other two coats, but signs of an inflammatory process were present here as well. There was some infiltration with lymphocytes and a few plasma cells could be seen, along with small numbers of epitheloid cells. The small branches of the artery outside the adventitia did not show any pathological changes. In both intima and media wide capillaries were present.

The picture is thus one of chronic granulomatous, giant-celled arteritis, affecting primarily the media of the artery, but showing changes in all three coats.

Summary

A case has been described in which the clinical and pathological findings are those of an arteritis of the temporal arteries. Perusal of the reports of similar cases suggests that temporal arteritis is but a local manifestation of a general disease of the arterial tree.

Our thanks are due to Mr. Warwick Bailey for the excision of the biopsy specimen, and to Drs. W. W. Woods and J. R. Gilmour for their opinions on the histological material.

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NICOTINIC ACID IN THE TREATMENT OF ANGINA PECTORIS

BY

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Glyceryl trinitrate has had no equal in the relief and prevention of the anginal attack. The claims of new drugs must, however, be tested if their pharmacological action includes dilatation of the coronary artery and if clinical benefit has been observed.

Since improvement in patients with angina pectoris has been reported recently by Moncrieff (1942) and Neuwahl (1942) from treatment with nicotinic acid, it became necessary to test the drug in a series of cases under controlled conditions. Moncrieff recorded benefit in three patients with doses varying from 10 to 50 mg. by mouth. Neuwahl claimed prolonged improvement in six patients after intravenous administration : one of these had received antisyphilitic treatment for aortitis, another showed aortic incompetence and great dilatation of the aorta, and a third with mitral stenosis was subject to paroxysmal auricular fibrillation ; electrocardiography was not a part of the examination, and no mention was made of the period of rest associated with the nicotinic acid infusions of which six were given within three weeks. Transient benefit was also claimed from oral administration of the drug, but no dosage was mentioned. Masek (1940) watched temporary improvement in four cases of old cardiac infarction, and in three with coronary sclerosis and angina pectoris, after the intravenous injection of the chloride of nicotinic acid in doses up to 0·16 g. He suggested that this effect might not only be due to coronary dilatation but also to an improvement in the metabolism of the myocardium by saturation with coenzymes.

The conversion of sugar to pyruvic acid and lactic acid occurs in a series of steps through intermediary substances so that a gradual supply of energy is liberated in the tissues (Eddy and Dalldorf, 1941). Involved in the type of oxidation which is based on hydrogen transfer, are many factors including " hydrogen acceptors," such as nicotinic acid amide. This is combined in the molecules of coenzyme I (diphospho-pyridine-nucleotide) and of coenzyme II (triphospho-pyridine-nucleotide) which are sometimes collectively termed the V factor. In man the administration of nicotinic acid causes a considerable rise in the level of the V factor in the blood (Kohn, Klein, and Dann, 1939) which should in theory assist the removal of lactic acid and other products of metabolism from the myocardium. If the accumulation of such substances plays some part in the causation of anginal pain, a rise in the coenzyme level of the blood and tissues should be beneficial in myocardial ischæmia. For this purpose the amide of nicotinic acid would be as efficacious as nicotinic acid itself, but would cause no vasodilatation (Field and Robinson, 1940).

Rachmilewitz and Braun (1944) discussing the cardiographic changes in nicotinic acid deficiency have assumed that an altered metabolic state of the heart is due to lack of coenzyme. In spite of the fact that the nicotinic acid intake on an average middle-class diet is perilously low (Kodicek, 1942), even minor degrees of deficiency must be very uncommon in this country. It is significant too, that I have found no reference to the common association of angina pectoris with pellagra, even in the elderly. In view of the possibility that an increment in coenzymes might mitigate the anginal pain, the amide of nicotinic acid has been employed as well as nicotinic acid in the present clinical trial.

The cutaneous response to nicotinic acid in the form of flushing has shown great variation not only in different subjects, but in the same subject at different times (Spies, Bean, and Stone, 1938 ; Sebrell and Butler, 1938). Although occasional flushing may result from doses as low as 25 mg., doses upward of 500 mg. are required to produce for certain a degree of peripheral effect. Experimental proof of general systemic vasodilatation and clinical observation in the

treatment of peripheral vascular disease have been disappointing. Popkin (1939) found that variations in surface temperatures were inconstant and that the amplitude of oscillometric readings actually diminished in most cases. Other investigators (Abramson, Katzenstein, and Senior, 1940) showed that a significant increase of blood flow was generally elicited in the hand and forearm with only a slight increase in the leg. As regards coronary dilatation there is as yet no definite evidence that this is produced by nicotinic acid. Quite apart from the inconstancy of vasodilatation as measured by peripheral flushing, the reaction does not take place for 10 to 20 minutes after the drug is taken by mouth and lasts a similar time. The peripheral effects, to say the least, are unpleasant ; and nicotinic acid on this account would be unpopular for routine use if flushing were an essential aim.

Description of Clinical Trial

In this investigation cases of angina pectoris were selected according to the criteria adopted by Evans and Hoyle (1933). Thus each patient had angina pectoris of effort, characterized by sub-sternal pain that spread across the chest, often through to the back, or to the shoulders, down one or both arms, or occasionally to the jaw and neck. The attack was always determined by physical exertion. Emotion sometimes induced an attack in some of the cases, but only where physical movement would bring on the pain as readily. Eight of the ten patients had had cardiac infarction at some previous date, but sufficient time had elapsed for maximum myocardial recovery to occur ; one of the remaining two had hypertension, and the other with classical anginal attacks had a normal cardiogram. All cases were studied as ambulant out-patients. Clinical examination included cardioscopy and cardiography and a Wassermann reaction was sometimes taken. The drugs given and doses employed are indicated in Table I. Each test period lasted at least one week, and this was often repeated. There was no particular sequence, and a placebo in the form of ascorbic acid or a gentian mixture was interspersed at intervals. All drugs were taken orally and swallowed, except for glyceryl trinitrate which was chewed. Nicotinic acid was employed in doses of 50 to 100 mg. prophylactically, and for the direct relief of the painful attack in some of the cases. In all cases during further trial periods it was given in regular doses of 25 or 50 mg., up to 200 mg. daily. Similarly nicotinamide was given in amounts up to 400 mg. in a day. It will be observed from the tabulated results that no greater benefit resulted from nicotinic acid or from nicotinamide than from a placebo. Improvement or deterioration that occurred during

Table I

Effect on pain in 10 patients with angina of nicotinic acid and nicotinamide compared with that obtained from placebo and glyceryl trinitrate

Drug	Dose and Method	1	2	3	4	5	6	7	8	9	10
Nicotinic Acid	50–100 mg. for relief and prevention.		—		—		—		+		
	Up to 200 mg. daily in 3 or 4 doses.	+	—	—	—	+	—	—	+	—	—
Nicotinamide	200–400 mg. daily in 4 doses.	—	+	+	—	—	+	+	—	—	—
Ascorbic Acid	For relief and prevention, 3–4 doses daily.	+	—	+	—	+	—	+	—	—	+
Gentian Mixture	Three doses daily.	+	+	—	—		—	—		—	
Glyceryl Trinitrate	For relief and prevention.	++	++	++	++	++	++	++	++	++	++

++ indicates great benefit ; +, slight benefit ; —, no benefit.

the trial periods could be explained by the natural variation in the severity and frequency of anginal attacks associated with or apart from changes in external influences. Thus, nicotinic acid failed to fulfil the postulates suggested by Evans (1944) as forming a statutory standard of efficiency for drugs. On the other hand great benefit was obtained in each patient from the use of glyceryl trinitrate ; it quickly relieved the attack when it had developed, and greatly reduced the number of attacks when a tablet was chewed before any exercise that customarily induced pain.

Toxic effects. Bean and Spies gave nicotinic acid to over a thousand subjects without toxic effects (Bicknell and Prescott, 1942). A fall in blood pressure from 190/100 to 110/80 was reported by Popkin (1939) after the administration of 100 mg. of nicotinic acid to a woman of 50 with essential hypertension. Other unpleasant effects after the oral administration of large doses have been reported, including true angor animi in one subject (Spies, Bean, and Stone 1938), dizziness, nausea, cramp in the epigastrium, vomiting, mental depression, palpitation, and urticaria. In the present trial severe flushing effects were reported by four patients. One felt tightness in the chest after a dose of 50 mg. and had to discontinue the drug because of faintness after taking eleven such doses within three days. His pain became worse. Another patient felt giddy after 50 mg., but later did not particularly mind a severe flushing reaction after 100 mg. The other two tolerated flushing well, but had no relief from pain. As expected, no such peripheral reactions occurred after nicotinamide.

Electrocardiographic Changes

Irregularities in the R–T segment and the T wave associated with anginal pain have been described by Parkinson and Bedford (1931) and by Goldhammer and Scherf (1932), but there

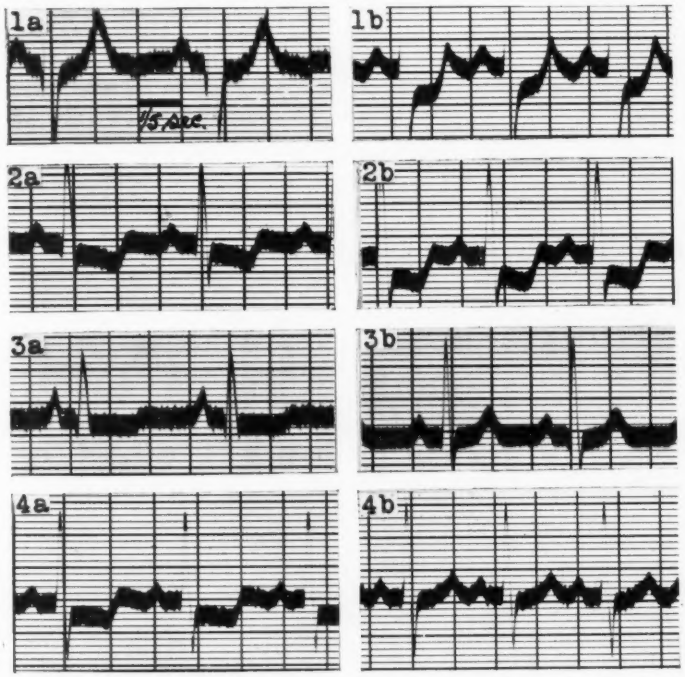

Fig. 1.—Changes in the electrocardiogram (lead IVR) of a patient with cardiac ischæmia, following the administration of nicotinic acid and glyceryl trinitate (see next page).

(1a) at rest. (1b) after exercise inducing pain.
(2a) at rest. (2b) 25 minutes after 200 mg. nicotinic acid which failed to cause flushing.
(3a) at rest. (3b) 24 minutes after 300 mg. nicotinic acid which caused generalized flushing.
(4a) at rest. (4b) 4 minutes after chewing glyceryl trinitrate gr. 1/100.

is a difference of opinion as to the frequency and character of such cardiographic variations (Freedberg *et al.*, 1941). These changes induced by anoxæmia have been employed by Levy and others (1939) as a test for coronary efficiency. Glyceryl trinitrate may correct such cardiographic variations (Evans and Hoyle 1933), so that the effect of nicotinic acid upon the abnormal electrocardiogram was tested in one case. In this patient exercise in the form of raising and lowering the legs to a standard height from the couch caused depression of the R–T segment.

The effect of nicotinic acid in preventing and correcting this deformity was observed and compared with that produced by glyceryl trinitrate (Fig. 1). When 200 mg. of nicotinic acid was given by mouth it did not cause flushing, neither did it prevent pain induced by exercise, nor R–T depression in the cardiogram. After 300 mg., which produced a severe flush, pain and R–T depression were prevented until the flush was passing. Absence of pain and cardiographic changes were noted on one occasion when flushing was induced by 150 mg. It has been widely assumed that depression of the R–T segment and inversion of the T wave associated with exercise are indications of coronary insufficiency. If these cardiographic changes are prevented by a drug administered before exercise, or corrected should they have already taken place, it might be reasonable to deduce that coronary blood flow has been improved thereby. Further observations on the effects of known coronary dilators on such cardiographic changes need to be carried out. Meanwhile these results appear to indicate that coronary dilatation does accompany the peripheral vascular effects of nicotinic acid, but that flushing is necessary and is variable in development even with large doses. After glyceryl trinitrate with the exception of periods when records were made at 4, 6, and 8 minutes after the tablet was chewed, exercise was continued until the patient was tired and breathless. No pain nor R–T depression resulted.

Conclusions

Changes in the electrocardiogram of cardiac ischæmia in man, following the administration of nicotinic acid, suggest that the drug can improve coronary blood flow; but this only results from a dosage large enough to produce peripheral flushing, which in itself is an uncertain and unpleasant effect.

In a controlled clinical trial no improvement resulted from the oral administration of nicotinic acid in moderate dosage, either in the prevention or relief of angina, and nicotinamide in larger doses failed to give better results.

Once again glyceryl trinitrate has shown that it has no equal in the treatment of angina pectoris, and nicotinic acid has no claim to routine use in this complaint.

I am indebted to Dr. William Evans for his advice in the preparation of this paper, and to Dr. E. Miles for facilities for the investigation.

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FIG. 1.—

PULMONARY EMBOLISM:

THE CLINICAL AND CARDIOGRAPHIC PROGRESS OF A CASE

BY

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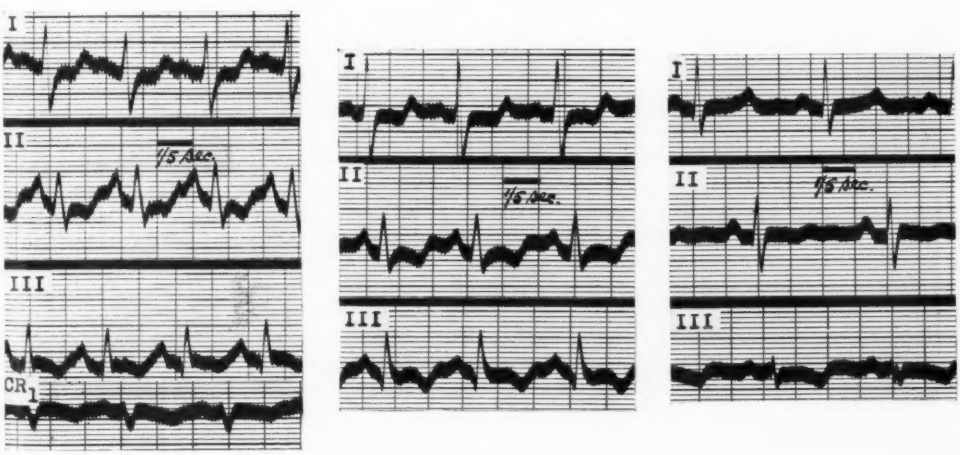
Although severe pulmonary embolism is not an uncommon complication of abdominal operations, the opportunities for a close clinical study of the condition are few. Too often the medical officer arrives at the bedside when it is too late. Even those patients who do not succumb at once rarely survive a few hours. In such circumstances, emergency measures connected with treatment take the place of clinical observations, which might include cardiographic records.

The account that follows is about a patient who developed severe pulmonary embolism, eight days after abdominal hysterectomy, and was observed continuously from the onset of the embolism until recovery took place.

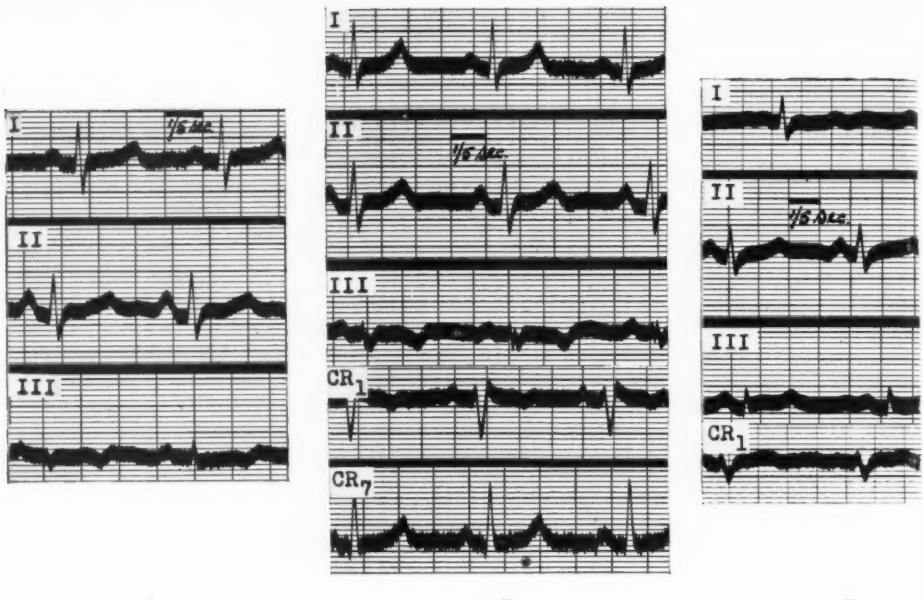
Case Notes

A woman, aged 42, was admitted to hospital for the investigation of ascites, which had lately set in with shortness of breath and anorexia. A hard and slightly tender nodular mass, rising out of the pelvis to the left of the midline, was considered to be an ovarian cyst and probably malignant. At laparotomy, free fluid was found in the peritoneal cavity; it had arisen in connection with papilliferous ovarian cysts, one of which had ruptured. The uterus, densely adherent to the bladder and rectum, was successfully removed with both cysts, which proved to be carcinomatous on microscopic examination.



A B C

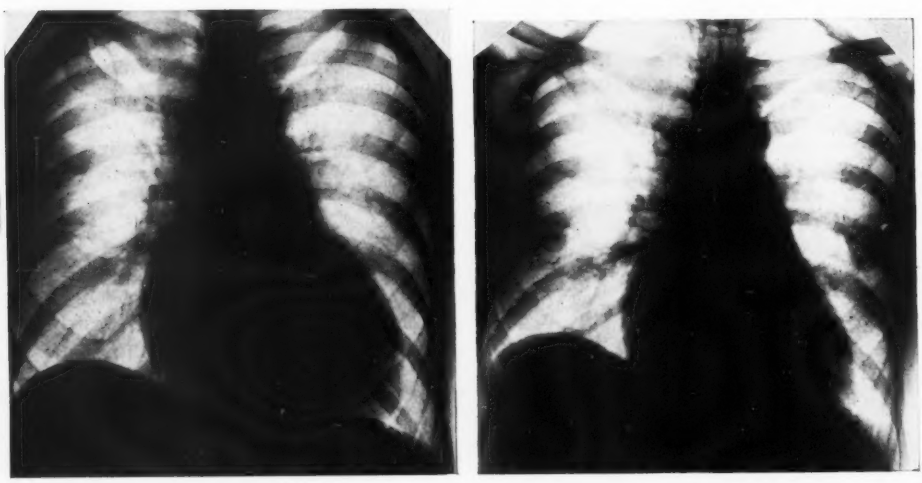
FIG. 1.—Serial cardiograms after pulmonary embolism (20/5/43), with inversion of T in leads II, III, and CR_1 (see p. 163).
(A) 20/5/43, the same evening. (B) 21/5/43, the next day. (C) 25/5/43.



A B C

FIG. 2.—Subsequent cardiograms showing recovery.
(A) 27/5/43, and (B) 1/6/43, with inverted T III. (C) 9/7/43, with upright T III.

On the eighth day after operation, the patient had a feeling of tightness across the chest and some breathlessness. The symptoms increased during the afternoon, and that evening the discomfort had given way to a feeling of suffocation. She called a nurse who noticed that the breathing had become distressed and that the pulse could not be felt. Five minutes later the patient became suddenly very dyspnœic and turned ashen grey. Gasping violently for breath, she called out " Give me air or I will die." Within thirty seconds she lost consciousness and became pulseless. The pupils dilated widely and the corneal reflex disappeared. There was spontaneous evacuation of urine and fæces.



A B

FIG. 3.—Teleradiograms showing cardiac enlargement, especially of the right side, and subsequent improvement.
(A) 21/5/43, fourteen hours after pulmonary embolism. (B) 27/5/43.

On auscultation of the heart, an obvious triple rhythm was heard, internal to the apex. Accurate placing of the additional heart sound was impossible at the time, owing to the severe tachycardia (140 a minute). The respiration, at first deep and rapid, became shallow and more rapid (40 a minute) during the period of unconsciousness, which lasted three minutes. The patient suddenly regained full consciousness, sweated profusely, and spoke in a whisper to those at the bedside. The pulse returned. In half an hour the respiration rate had returned to 18 a minute and distress was absent, although exhaustion was still present. The pulse continued to be small and rapid (132 a minute) and the blood pressure was 90/80. The apex beat could not be felt. The heart sounds were distant and there was accentuation of the pulmonary second sound. The triple rhythm persisted.

Next day the patient's condition deteriorated rapidly; the pulse rate dropped from 120 to 76, and the respirations became slow and deep ; but these changes did not last and improvement again took place. With the slower heart rate it was possible to tell that the triple rhythm was caused by the addition of the third heart sound. The blood pressure also improved to 115/75. Harsh breath sounds were heard over the midzone of the left lung but no dullness or moist sounds developed. There was great improvement in the patient's condition on the third day and her recovery appeared to be assured. On the fourth day after pulmonary embolism triple rhythm gave way to dual rhythm, and the blood pressure rose to 130/85. The patient remained apyrexial throughout the illness. There was at no time any complaint of cough or sharp pain in the chest, and hæmoptysis was absent. Oxygen was administered from the onset of the illness and was continued for 25 hours. In the hope of preventing the spread of thrombosis 20,000 units of heparin were administered intravenously on the first day, and 5,000 units two hourly for four doses when di-coumarin (100 mg. by mouth daily for 14 days) was substituted. With the object of decreasing arterial spasm at the site of the embolus, 1 c.c. of eupaverin was given intramuscularly 4-hourly for four doses. Frequent cardiograms were recorded throughout the illness. They confirmed the diagnosis of sudden failure of the right heart and served as an index of recovery of the heart. The serial tracings (Fig. 1 and 2) showed right ventricular preponderance and inversion of the T waves in leads II, III, and in CR_1 ; the T wave in CR_7 was upright. Serial teleradiograms (Fig. 3) were also taken and these showed alteration in the size of the heart contingent with the severity and duration of the obstruction in the pulmonary circulation. They failed to reveal any evidence of pulmonary infarction.

Discussion

The observations of McGinn and White (1935) that consistent variations from the normal appeared in the cardiograms of a number of their patients developing pulmonary embolism have given impetus to the study of the behaviour of the heart in this condition. Their results have been repeatedly confirmed and extended by numerous workers, particularly by Barnes (1936), who tabulated in detail the diagnostic features of the limb lead changes occurring in pulmonary embolism, and by Wood (1941), who directed attention to the significance and importance of multiple chest leads in the differential diagnosis of acute cor pulmonale. In spite of these notable advances, as Murnaghan and others (1943) have pointed out in a review of 102 cases of pulmonary embolism, confusion is liable to arise in an interpretation of the cardiographic changes, unless a distinction is made between cases with and without acute cor pulmonale and cases with and without pre-existing heart disease. Furthermore it is only by assigning a case of pulmonary embolism to its appropriate category that a correct interpretation of the clinical and cardiographic findings is possible. The case reported, having developed a severe degree of acute cor pulmonale in the absence of pre-existing heart disease, affords a good opportunity for undisturbed observation of the effects on the heart of pulmonary embolism, and has allowed its close study which has already extended over twelve months. In addition, certain clinical observations, dating from the moment of embolism, early cardiographic tracings and serial radiograms of the heart have yielded information in regard to the mechanism of acute cor pulmonale.

Pulmonary obstruction compatible with survival. Experimental evidence would indicate that pulmonary obstruction may be considerable without extinguishing life. Thus, Haggart and Walker (1923) by quantitative closure of the pulmonary artery in cats found that, when up to 52 per cent of the lumen was occluded, few ill-effects were observed, but that when occlusion exceeded 66 per cent the animals invariably died. Clamping the left pulmonary artery raised the pulmonary arterial pressure by 29 per cent and the respiratory rate by 25 per cent without

altering the size of the heart, the cardiac output, or the systemic arterial blood pressure. From the clinical aspect, the findings of Thompson and Evans (1930) show that the upper limit of acute depletion of the pulmonary circulation compatible with survival, is under 50 per cent. Studying the problem of paradoxical embolism and its relation to pulmonary embolism, they concluded that if 50 per cent or more of the pulmonary circulation be cut off suddenly by an embolus, death results within 10 to 30 minutes. Thus in 18 cases of pulmonary embolism, in which embolus was the cause of death proved at autopsy, 16 showed depletion of the pulmonary circulation by 50 per cent or more ; only one of these 16 cases had survived a period of 30 minutes.

Severe pulmonary obstruction without infarction. The clinical, radiological, and cardiographic evidence in the case reported, indicates severe initial pulmonary obstruction which became steadily regressive and finally ceased. The most likely explanation for this behaviour —applicable to other cases of acute cor pulmonale which survive—is that much of the severe but temporary obstruction is caused by vasospasm throughout the pulmonary tree as a result of the embolism (Jesser and de Takáts, 1941). This explanation is rendered all the more certain in the present case, in that there was neither clinical nor radiological evidence of pulmonary infarction. Such negative evidence would also indicate that the embolus initiating pulmonary obstruction was of small size. It is not easy to envisage an embolus that could bring about a severe degree of obstruction by virtue of size alone being driven into the pulmonary tree and yet failing to produce an infarct. But even allowing that the embolus were small, why did it not declare itself by signs of pulmonary infarction ? The only explanation accounting for such a contingency is found in the unusually rich anastomosis existing between the bronchial and pulmonary arteries, preventing pulmonary infarction. Anastomoses of this kind, an exaggeration of the normal, are seen for example in a gross and chronic form in congenital pulmonary atresia.

The clinical diagnosis of acute cor pulmonale. McGinn and White (1935) described acute cor pulmonale as the result of sudden distension of the right ventricle and right auricle which might follow obstruction to the pulmonary artery by an embolus. The condition can frequently be recognized by a knowledge of the previous history and by attention to the early symptoms and signs as typified by the present case. Severe initial shock, pallor, cold extremities, great dyspnœa, and low blood pressure are important signs in the clinical diagnosis of acute cor pulmonale. Thus Murnaghan and others (1943) in two series of cases of pulmonary embolism, presenting with and without signs of shock, found cardiographic evidence of acute cor pulmonale in just over half of the first group and in under a quarter of the second. Distension of cervical veins, although not recorded in the present case, is claimed by Wood (1941) to be present in all cases of acute cor pulmonale in which this sign is sought within the first three days of embolism. After this period venous distension is often absent.

A physical sign of great diagnostic value is the early appearance of triple rhythm due to the third heart sound. Within a few minutes of embolism in the present case a distinct triple rhythm was heard, and although its exact nature during tachycardia was difficult to interpret it became obvious when the beat slowed. Triple rhythm in acute cor pulmonale has been recorded by several observers (Murnaghan *et al.*, 1943 ; Wood, 1941), but without emphasis on its value in clinical diagnosis. The addition of the third heart sound, when not a physiological finding in young adults, is a reliable clinical index of right-sided heart failure (Evans, 1943). Thus it was commonly heard in mitral stenosis, hypertensive heart failure, emphysema, and congenital heart disease.

The early appearance of the third heart sound in the present case was clinical proof of acute cor pulmonale because of the known absence of previous heart disease. This sign should rank high amongst the clinical criteria by which the diagnosis of acute cor pulmonale is determined. Less severe pulmonary embolism producing lesser degrees of acute cor pulmonale may not show triple rhythm, and recourse to electrocardiographic records may be necessary

to supply evidence of right ventricular stress, but it suggested that every case of pulmonary embolism presenting triple rhythm (Type Ib of Evans) demonstrates acute cor pulmonale as well, provided that pre-existing heart disease can be excluded.

Changes in the size of the heart. Cardiac enlargement, predominantly of the right side, shown radiologically 14 hours after embolism (Fig. 3), would indicate that actual distension of the right ventricle and right auricle was an important factor in determining the striking initial cardiographic changes, which persisted in a modified and steadily regressive form for a period of seven weeks. Besides demonstrating that acute ventricular distension, compatible with survival, can take place in the absence of radiographic evidence of pulmonary infarction, the X-ray appearance of the heart is in keeping with the post-mortem findings of right ventricular and right auricular enlargement evidenced in some fatal cases of pulmonary embolism.

Electrocardiographic changes. Cardiographic irregularities in pulmonary embolism are characteristic, and when present they confirm the presence of acute cor pulmonale. Briefly they are, prominent S I with the S–T segment starting slightly below the base line ; depressed RS–T segment in lead II, with gradual ascent from the S to the T wave in the same lead ; usually a diphasic or monophasic T II; the presence of a Q wave and definite inversion of T in lead III (McGinn and White, 1935) ; sharp inversion of T without appreciable displacement of the RS–T segment, always in CR_1, and sometimes for shorter duration in IV R ; T in CR_1 commonly remains inverted for several weeks ; less essential is a tendency for the QRS deflection to be mainly upward in CR_1 (Wood 1941).

My case showed such changes, some of them strikingly. Right axis deviation was noteworthy, with an unusually deep S I and sharp inversion of T in leads II, III, and CR_1. Thus the cardiographic records confirmed the conclusions reached in regard to the early appearance of the third heart sound and the radiographic evidence of right ventricular distension. The chest leads show that recovery was delayed longest in CR_1, and that even after seven weeks, the T wave although upright was low. Thus, T in CR_1 is the most sensitive cardiographic index we possess for determining the presence of right ventricular strain. The direction of the T wave in lead CR_7 should be noted. Evans and Hunter (1943) in describing this lead implemented it in distinguishing between T II and T III inversion of posterior cardiac infarction and similar changes seen in heart failure in emphysema and in pericardial and congenital heart disease. In these conditions T in CR_7 is positive, with recognized exceptions, while the reverse is usually the case in posterior cardiac infarction. In my case, therefore, a positive T in CR_7 demonstrates that their observations apply equally to a condition characterized by acute right ventricular failure as they do to the chronic forms of right sided failure which they described.

Myocardial ischæmia—resulting from coronary insufficiency and variously attributed to increased tension in the right ventricle, shock, asphyxia, fall in systemic arterial pressure, and reflex changes in the coronary circulation—has been put forward to account for the cardiographic changes in pulmonary embolism (Horn *et al.*, 1939). Although cardiac ischæmia undoubtedly takes place in the development of acute cor pulmonale and may even proceed to cardiac infarction, in the absence of coronary occlusion (Currens and Barnes, 1943), it cannot be advanced as the cause of the limb lead changes. Wood (1941) had demonstrated that although the limb lead changes in pulmonary embolism and posterior cardiac infarction may simulate each other, the chest lead changes in the two conditions are entirely different. More recently (Evans and Hunter, 1943) the CR_7 chest lead has helped in the differential diagnosis as instanced by my case. Further, the similarity of cardiographic behaviour in pulmonary embolism and in conditions characterized by chronic right ventricular strain, points to acute right ventricular stress as being the cause of the cardiographic changes in pulmonary embolism. Cardiographic changes similar to those seen in pulmonary embolism may be recorded in pulmonary stenosis, mitral stenosis, and chronic cor pulmonale (Selzer and Wood, 1939), while in rheumatic carditis, which may be associated with isolated right ventricular failure, Wood

(1941) has recorded transient changes, indistinguishable from those found in pulmonary embolism.

Summary and Conclusions

A case of pulmonary embolism with acute cor pulmonale is described. A severe degree of cor pulmonale developed in the absence of radiological evidence of pulmonary infarction.

Emphasis has been placed on the value of triple rhythm, from the addition of the third heart sound, in the diagnosis of suspected cases of pulmonary embolism.

Radiographic evidence of distension of the right auricle and right ventricle is related to the onset and duration of the cardiographic changes. Inversion of the T wave in CR_1 is probably the most sensitive of the cardiographic indices of right ventricular failure. The value of this change and of findings in lead CR_7 in the diagnosis of acute cor pulmonale from posterior cardiac infarction is confirmed.

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